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Stereocontrolled Formation of Spiroenones by Radical Cyclization of Bromoacetals and the Synthesis of Cladobotryal and 2-*epi*-CJ-16,170

by

Xiaojun Huang ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Stereocontrolled Formation of Spiroenones by Radical Cyclization of Bromoacetals and the Synthesis of Cladobotryal and 2-*epi*-CJ-16,170** submitted by **Xiaojun Huang** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Sept. 24, 2003

Dr. G. J. Bodwell
(External Examiner)

To

my wife, Guifeng Jiang,

my son, Jiajie Michael Huang,

and my parents

ABSTRACT

The first part of this thesis describes aldol condensation of ketones with 2-[[1,1-(dimethylethyl)-diphenylsilyl]oxy]propanal. Dehydration, $NaBH_4$ reduction and treatment of the resulting alcohols with ethyl vinyl ether in the presence of NBS gave bromoacetals that underwent 5-*exo*-trigonal radical cyclization, affording compounds that were easily converted into spiroenones. The stereochemistry at the spirocenter was controlled by the stereochemistry at the hydroxyl-bearing carbon of the intermediate alcohol.

The second part of this thesis deals with synthetic studies on the antifungal and antibacterial agent cladobotryal, a metabolite of the fungus *Caldobotrium varium* Nees:Fries (CBS 331.95). Cladobotryal contains two contiguous stereogenic centers, one of which is an asymmetric quaternary carbon, and represents a new compound class. Cladobotryal was synthesized by a convergent route. Radical cyclization generated the quaternary center with stereochemical control by an adjacent stereogenic center. A key step in elaboration of the pyridinone ring was conversion of a Boc group on nitrogen into a $CO_2SiPr\text{-}i_3$ group. The synthesis of a stereoisomer (2-*epi*-CJ-16,170) of the natural furopyridinone antibiotic CJ-16,170 is also described.

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I would like to express my gratitude to Dr. D. L. J. Clive for his constant support, encouragement and advice during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

I would also like to thank all group members and friends for their useful discussions and support. In particular, I would like to acknowledge Dr. Shaoyi Sun, Dr. Vince Yeh and Dr. Shunzhen Kang for their generous assistance during the initial stages of my laboratory work.

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List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOC	based on conversion
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
Bu	butyl
t-Bu	*tert*-butyl
CAN	ammonium cerium(IV) nitrate
cf.	compare
^{c}Hex	cyclohexyl
Cp	cyclopentadiene
CpCOOR	camphanate
dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Dess-Martin reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-3(1*H*)-one
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine

DME	ethylene glycol dimethyl ether
DMF	*N*,*N*'-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphanyl)ethane
EDCI	*N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
Et	ethyl
Fmoc	fluorenylmethoxycarbonyl
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexmethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyl-thiouronium hexafluorophosphate.
Hz	Hertz
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LN	lithium naphthalenide
Me	methyl
MEM	2-methoxyethoxymethyl
min	minute(s)
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
o-tol	*o*-tolyl
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PIFA	phenyliodine(III) bis(trifluoroacetate)
PPTS	pyridinium *p*-toluenesulfonic acid
pro	proline
pyr	pyridine
SEM	2-(trimethylsilyl)ethoxymethyl
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
p-TSA	see TsOH
TsOH	*p*-toluenesulfonic acid

CHAPTER 1

Stereocontrolled Formation of Spiroenones by Radical Cyclization of Bromoacetals

1 INTRODUCTION

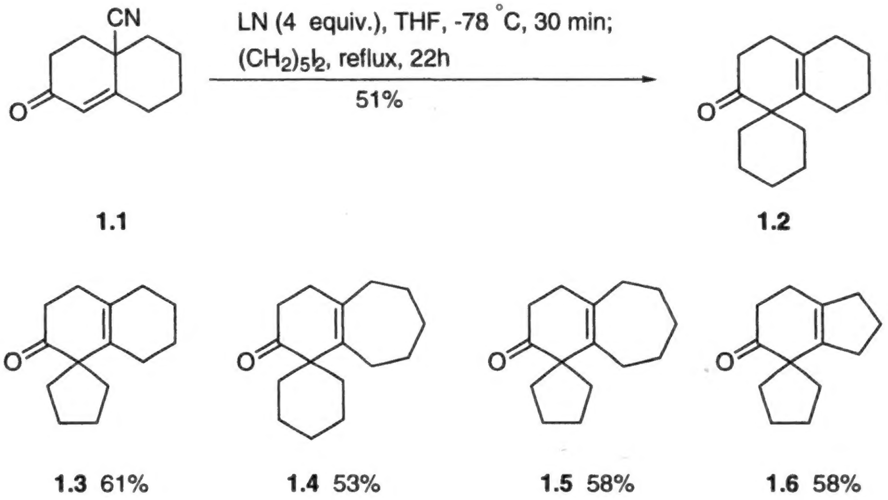
A number of biologically active natural products contain spirocycles with quaternary carbon stereocenters,[1] that is, carbon centers with four different non-hydrogen substituents. The regio- and stereocontrolled generation of quaternary carbon centers is still a formidable challenge in organic synthesis. The methods that have been used for stereoselectively controlled formation of spirocompounds involve alkylation, transition-metal based processes, rearrangement, ring closure of geminally disubstituted starting materials, cycloaddition, and radical cyclization as the key step. These approaches were reviewed in great detail by Sannigrahi in 1999.[1a]

Since that review, additional work has appeared, and is discussed below.

1.1 Use of alkylation

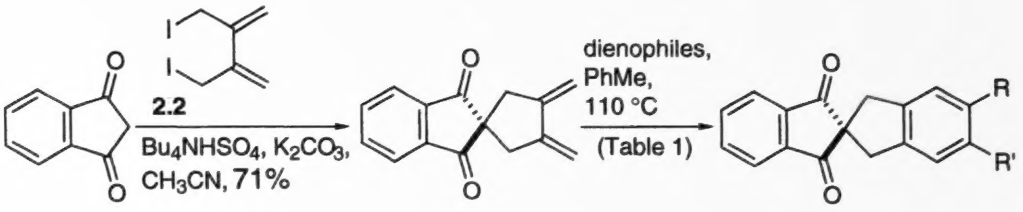
a. Intramolecular alkylation

Liu *et al.*[2] have investigated a modified Robinson annulation for the construction of α,α-disubstituted-β,γ-unsaturated spirocyclic compounds, starting with readily available α-cyano-activated cycloalkenone derivatives (Scheme 1). Reductive spiro-annulation was achieved by treatment of γ-cyano-α,β-unsaturated cyclohexenones with lithium naphthalenide (LN) and an α,ω-dihaloalkane. The formation of spirocompound **1.2** could be effected by treatment of cyanoenone **1.1** with LN (4 equiv) in THF at -78 °C for 30 min, followed by addition of 1,5-diiodopentane (2 equiv). The spiro ring formation was more effective when performed at elevated temperature: 51% in refluxing THF, 35% at room temperature. Spirocompounds **1.3**-**1.6** were prepared similarly.


CN
O
LN (4 equiv.), THF, -78 °C, 30 min;
(CH2)5I2, reflux, 22h
51%
O
1.1
1.2
O
O
O
O
1.3 61%
1.4 53%
1.5 58%
1.6 58%

Scheme 1

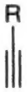
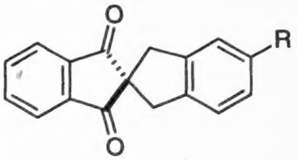
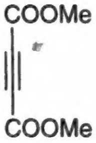
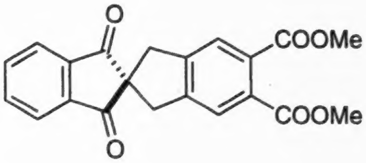
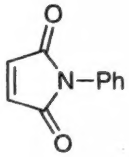
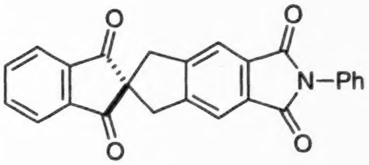
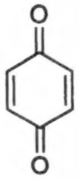
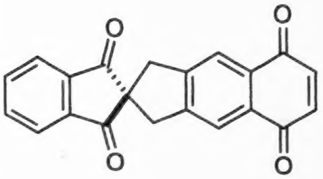
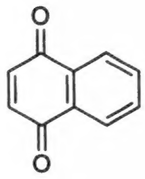
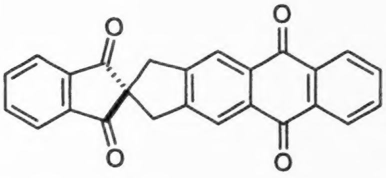
Kotha and Manivannan[3] prepared several spirobiindanediones (**2.4**) using intramolecular alkylation, followed by Diels-Alder reaction (Scheme 2). Alkylation of the indanedione **2.1** with the highly sensitive 2,3-bis(iodomethyl)buta-1,3-diene (**2.2**) under phase transfer catalysis [K_2CO_3, dry MeCN, Bu_4NHSO_4 at room temperature] gave the diene **2.3**, and further reaction with various dienophiles gave the aromatized product **2.4** in moderate to good yields (Table 1).


O
O
I
I
2.2
Bu$_4$NHSO$_4$, K$_2$CO$_3$, CH$_3$CN, 71%
O
O
dienophiles, PhMe, 110 °C
(Table 1)
O
O
R
R'

2.1 2.3 2.4

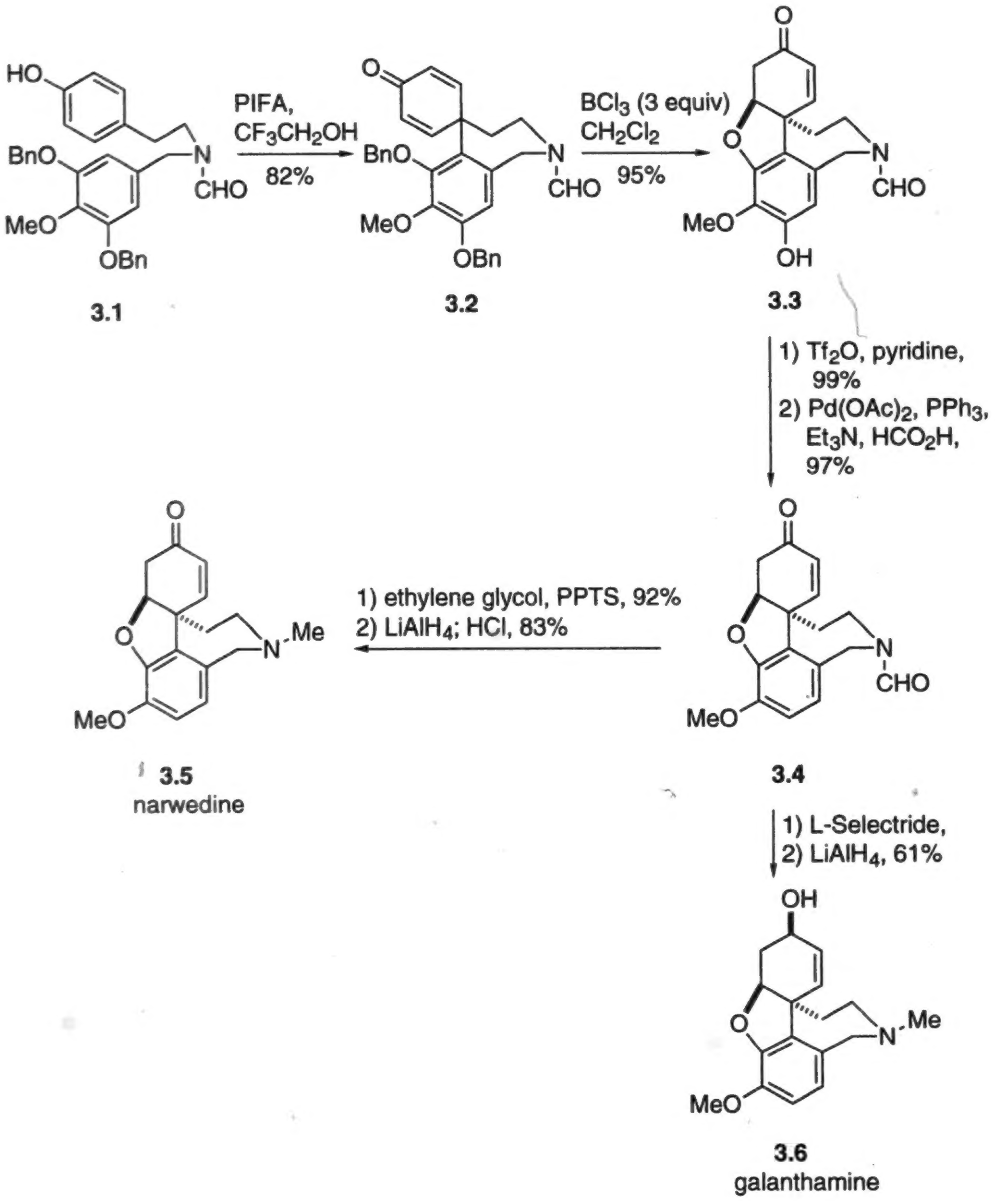
Scheme 2

Table 1. Various spiro-indanes prepared by cycloaddition strategy

Dienophile/Monoyne	Spiro product		Yield (%)
		R = COOMe	53
		R = Ts	54
		R = TMS	87
 COOMe COOMe	 O COOMe COOMe O		87
			65
			45
			75

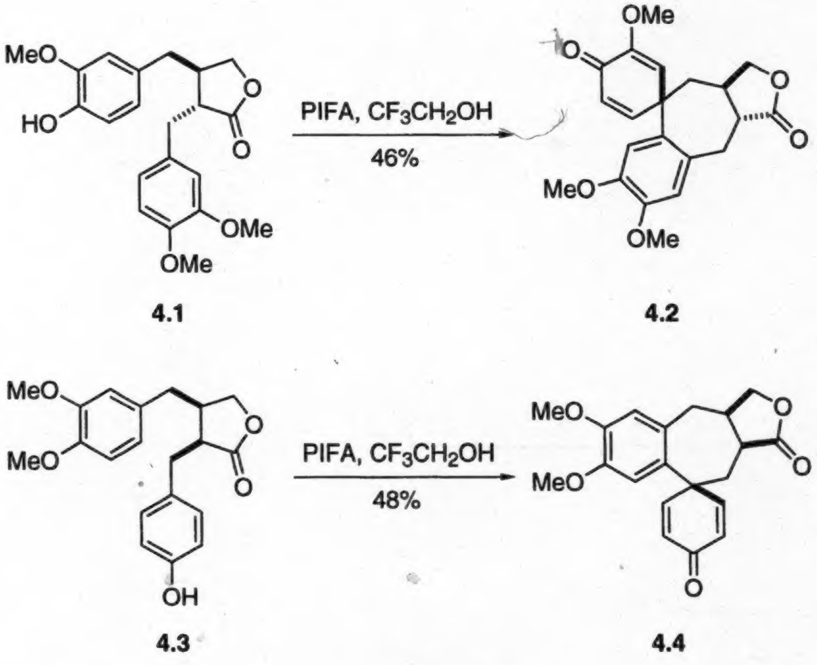
b. Phenolic oxidative cyclization

Node's synthesis[4] of (±)-narwedine (**3.5**) and (±)-galanthamine (**3.6**) utilized an improved phenolic oxidative coupling as the key step (Scheme 3). Oxidative coupling of


HO
BnO
MeO
OBn
N
CHO
3.1
PIFA, CF3CH2OH
82%
O
BnO
MeO
OBn
N
CHO
3.2
BCl3 (3 equiv)
CH2Cl2
95%
O
O
N
CHO
MeO
OH
3.3
1) Tf2O, pyridine, 99%
2) Pd(OAc)2, PPh3, Et3N, HCO2H, 97%
O
O
N
CHO
MeO
3.4
1) ethylene glycol, PPTS, 92%
2) LiAlH4; HCl, 83%
O
O
N
Me
MeO
3.5
narwedine
1) L-Selectride,
2) LiAlH4, 61%
OH
O
N
Me
MeO
3.6
galanthamine

Scheme 3

the norbelladine-type derivative **3.1**, using PhI(OCOCF$_3$)$_2$ [phenyliodine(III) bis(trifluoroacetate) (PIFA)] as the oxidant in CF$_3$CH$_2$OH, produced spirodienone **3.2** in good yield. Selective removal of the benzyl protecting groups in the presence of the methyl ether was achieved by using relatively weak acid conditions (BCl$_3$ in CH$_2$Cl$_2$ at -78 °C). The desired narwedine-type product **3.3** was produced in excellent yield (95%) by an intramolecular 1,4-addition. The extra hydroxy group in **3.3** was reduced in 97% yield by its conversion into a triflate group, followed by Pd(0)-catalyzed reduction with HCO$_2$H. Compound **3.4** was converted efficiently into (±)-narwedine (**3.5**) by protection of the ketone group, followed by reduction of the *N*-formyl group to an *N*-methyl group and

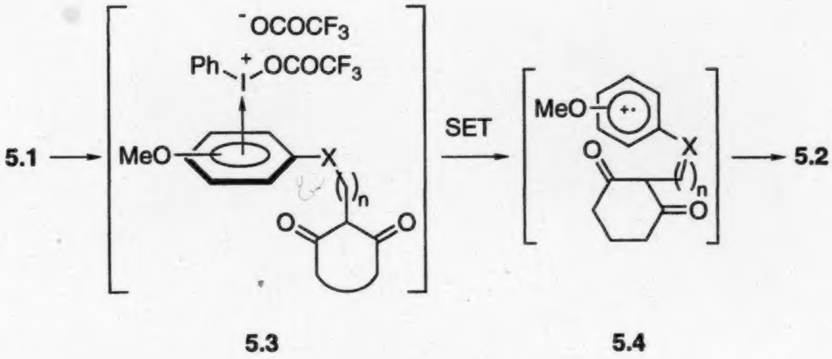

MeO
HO
O
O
OMe
OMe
PIFA, CF3CH2OH
46%
OMe
O
O
O
MeO
OMe
4.1
4.2
MeO
MeO
O
O
OH
PIFA, CF3CH2OH
48%
MeO
MeO
O
O
O
4.3
4.4

Scheme 4

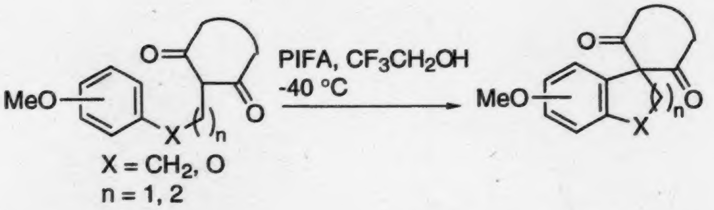
deprotection of the ketal. Compound **3.4** was also transformed into (±)-galanthamine (**3.6**) by diastereoselective reduction of the carbonyl, followed by reduction of the *N*-formyl group to an *N*-methyl group.

Ward and Hughes[5] also found that the spirodienones **4.2** and **4.4** could be prepared in moderate yield by the action of PIFA in CF_3CH_2OH (Scheme 4).

Kita *et al.*[6] examined a number of PIFA-induced intramolecular reactions of *para*- and *meta*-substituted phenol ethers (**5.1**) to make substituted spirobenzannulated compounds **5.2** (Table 2), and they also proposed the mechanisms for their reactions (Scheme 5). Phenol ether derivatives **5.1** react with PIFA to form charge-transfer complexes **5.3**. Single electron transfer (SET) affords the cation radicals **5.4**, which then undergo cyclization to give the products **5.2**.

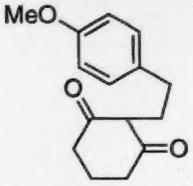
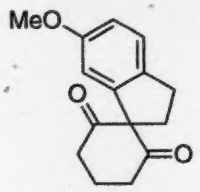
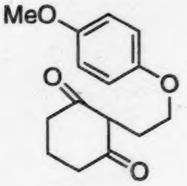
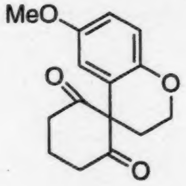
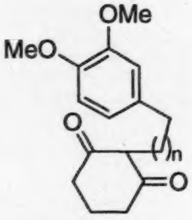
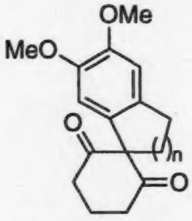
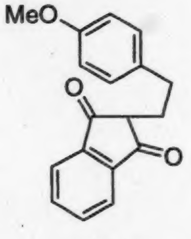
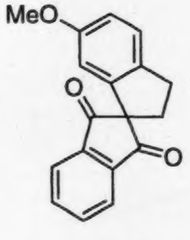
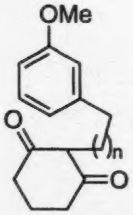
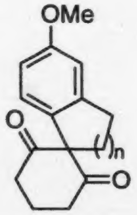


Scheme 5


MeO
X
n
O
O
PIFA, CF3CH2OH
-40 °C
MeO
X
n
O
O
X = CH2, O
n = 1, 2

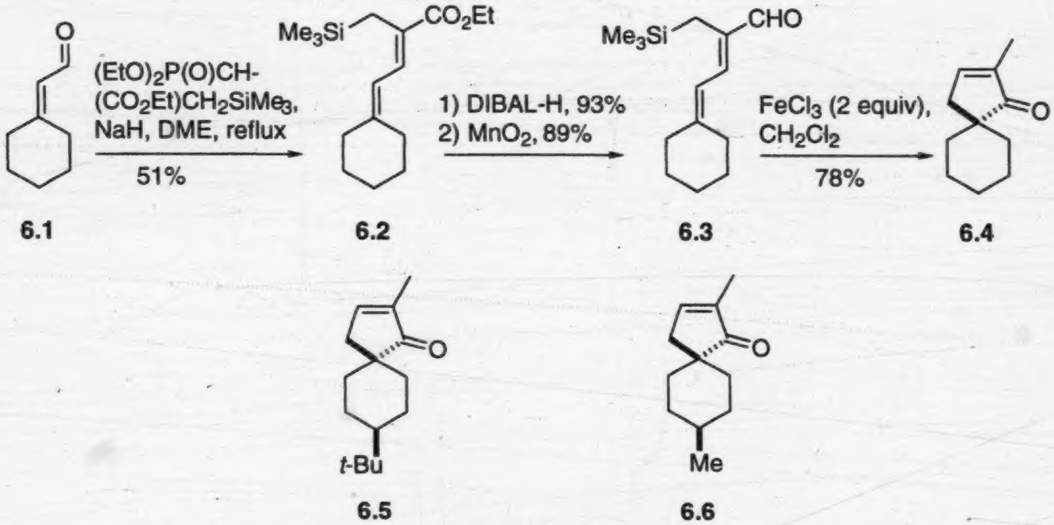
5.1 **5.2**

Table 2 PIFA-induced intramolecular reaction of *para*- and *meta*-substituted phenol ether derivatives

Substrate (**5.1**)	Product (**5.2**)	Yield (%)
		85
		65
		39 (n = 1) 70 (n = 2)
		34
		70 (n = 1) 69 (n = 2)

c. *Lewis acid induced Nazarov self-cyclization*

Kuroda and Koshio[7] reported a new self-cyclization to afford spiro[4,5]decane ring systems **6.4** starting from allylsilanes (Scheme 6). Aldehyde **6.1** was converted into the β-(ethoxycarbonyl)allylsilane **6.2** in 51% yield. DIBAL-H reduction of **6.2** (92%), followed by MnO_2 oxidation, afforded allylsilane aldehyde **6.3** (89%), which was cyclized by treatment with ca 2 equiv of $FeCl_3$ in CH_2Cl_2 at room temperature. The spiro[4,5]decane **6.4** was isolated in 78% yield. Spirocompounds **6.5** and **6.6** were prepared similarly. The reaction mechanism was not understood.

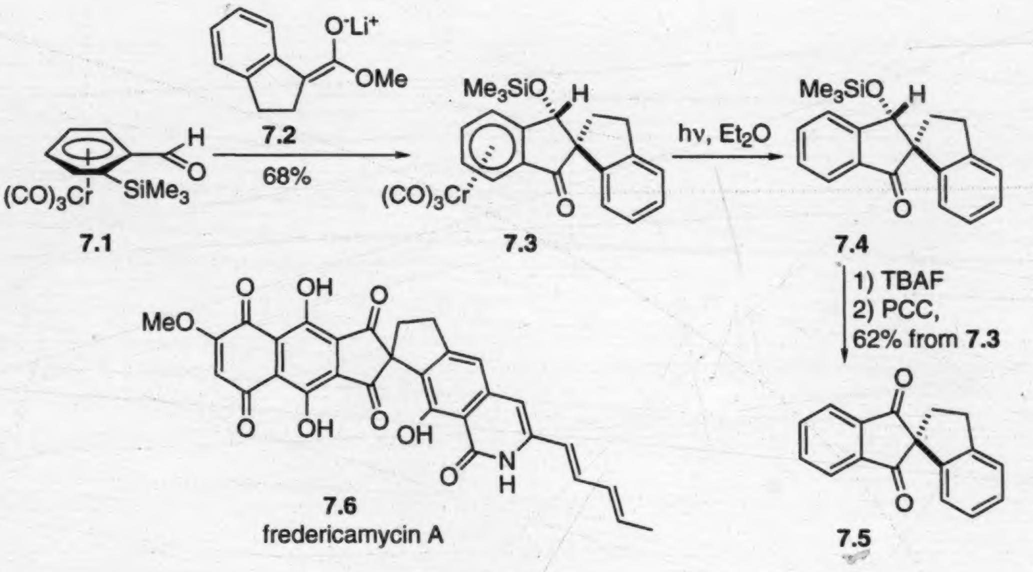

O
(EtO)2P(O)CH-
(CO2Et)CH2SiMe3,
NaH, DME, reflux
51%
6.1
Me3Si
CO2Et
6.2
1) DIBAL-H, 93%
2) MnO2, 89%
Me3Si
CHO
6.3
FeCl3 (2 equiv),
CH2Cl2
78%
O
6.4
O
t-Bu
6.5
O
Me
6.6

Scheme 6

1.2 Transition Metal-Based Processes

a. *Use of (arene)tricabonyl chromium(0) complexes*

Moser[8] has explored the use of arene chromium tricarbonyl complexes in the stereoselective synthesis of the spirocyclic core of fredericamycin A (**7.6**). Aldol addition of lithium enolate **7.2** to arene chromium tricarbonyl complex **7.1** provided the corresponding chromium tricarbonyl-complexed indanone **7.3**. Quantitative removal of the chromium fragment was conveniently achieved by exposure to air and sunlight to afford product **7.4**. Desilylation, followed by PCC oxidation, provided the spirocyclic core **7.5** of fredericamycin A. The observed stereochemistry was generated since the chromium tricarbonyl group effectively blocks the complexed face of the arene complex **7.1**.

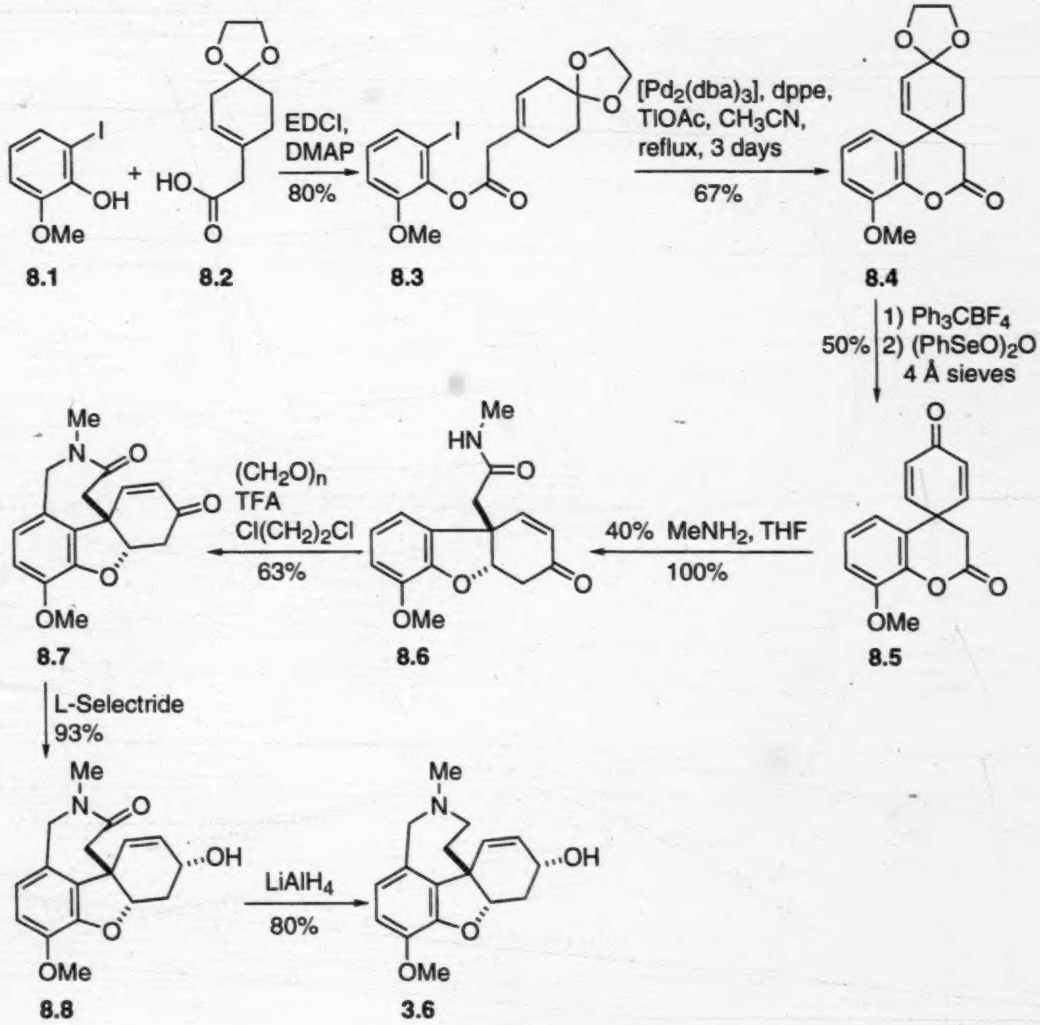


O⁻Li⁺
OMe
7.2
68%
H
O
(CO)3Cr
SiMe3
7.1
Me3SiO
H
(CO)3Cr
O
7.3
hν, Et2O
7.4
1) TBAF
2) PCC,
62% from 7.3
7.5
MeO
OH
OH
N
H
7.6
fredericamycin A

Scheme 7

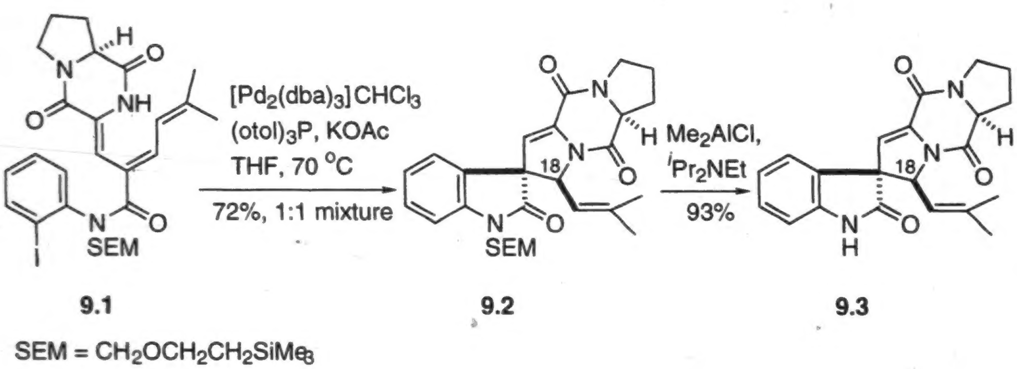
b. Palladium-based methods

In Guillou's synthesis[9] of (±)-galanthamine (**3.6**), the palladium catalyzed intramolecular Heck reaction was applied to generate the spiro quaternary center. Esterification of acid **8.2** with 2-iodo-6-methoxyphenol (**8.1**) furnished the ester **8.3**. Heck cyclization of **8.3** was accomplished in 65% yield in the presence of 10% [$Pd_2(dba)_3$], 20% dppe, and TlOAc (1.2 equiv) in MeCN. This compound was converted into (±)-galanthamine (**3.6**) in six steps (Scheme 8).



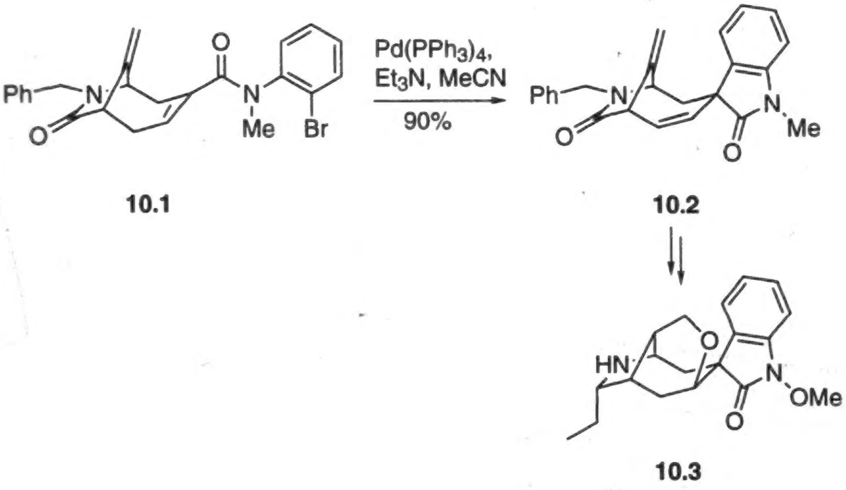
8.1
8.2
EDCI, DMAP
80%
8.3
[$Pd_2(dba)_3$], dppe, TlOAc, CH_3CN, reflux, 3 days
67%
8.4
1) Ph_3CBF_4
2) $(PhSeO)_2O$
4 Å sieves
50%
8.5
40% $MeNH_2$, THF
100%
8.6
$(CH_2O)_n$
TFA
$Cl(CH_2)_2Cl$
63%
8.7
L-Selectride
93%
8.8
$LiAlH_4$
80%
3.6

Scheme 8


[Pd$_2$(dba)$_3$]CHCl$_3$
(otol)$_3$P, KOAc
THF, 70 °C
72%, 1:1 mixture
Me$_2$AlCl,
^{i}Pr$_2$NEt
93%
18
SEM
9.1
9.2
9.3
SEM = CH$_2$OCH$_2$CH$_2$SiMe$_3$

Scheme 9

In the synthesis of (-)-spirotryprostatin B (**9.3**), Overman[10] used two palladium-catalyzed reactions: Heck insertion and trapping of an η^3-allylpalladium intermediate by a nitrogen nucleophile. Cyclization of the advanced intermediate **9.1** with 10% [Pd$_2$(dba)$_3$]·CHCl$_3$, 40 mol% tri-*o*-tolylphosphine, and excess AcOK in THF at 70 °C cleanly led to the formation of a 1:1 mixture of spirocyclic compounds **9.2** and the C-18 epimer. Removal of the SEM group from **9.2**


Pd(PPh$_3$)$_4$,
Et$_3$N, MeCN
90%
10.1
10.2
10.3

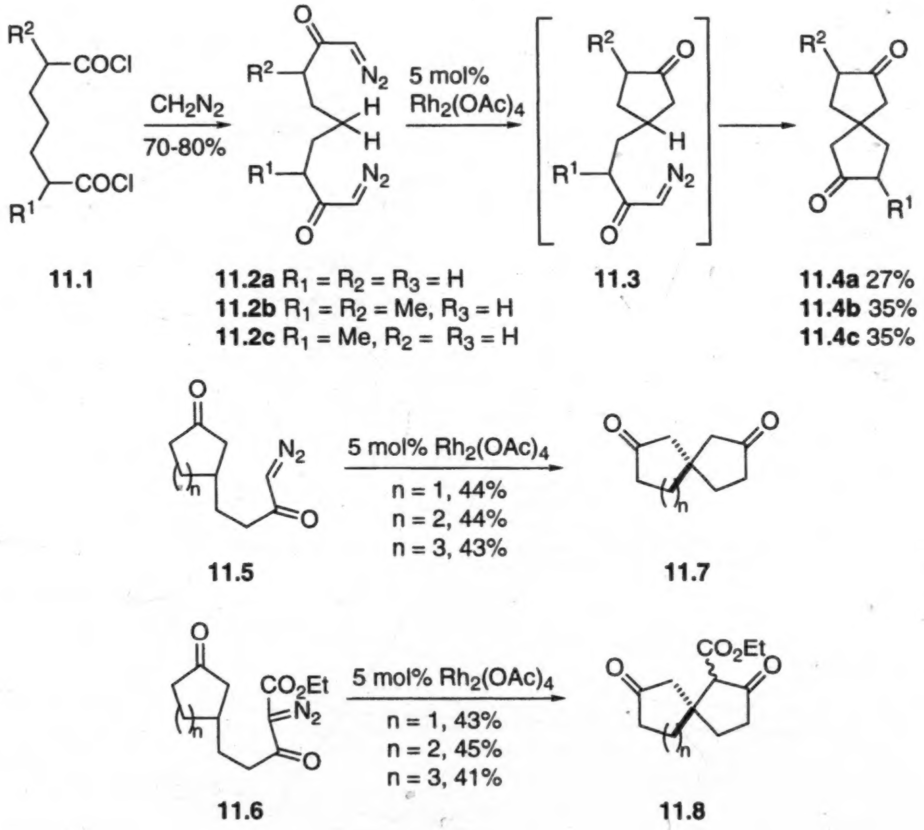
Scheme 10

provided (-)-spirotryprostatin B (**9.3**).

Hiemstra[11] also used a palladium mediated Heck reaction in the synthesis of *ent*-gelsedine (**10.3**) (Scheme 10). Heck cyclization of **10.1** [($Pd(PPh_3)_4$, Et_3N, MeCN, 100-120 °C, sealed tube] gave spirocompound **10.2**, and this served as one of the key steps in the total synthesis of *ent*-gelsedine (**10.3**).

c. Rh(II)-catalyzed methods

Undheim[12] described the synthesis of β-oxospirane systems by rhodium(II)-carbenoid C-H insertion reactions

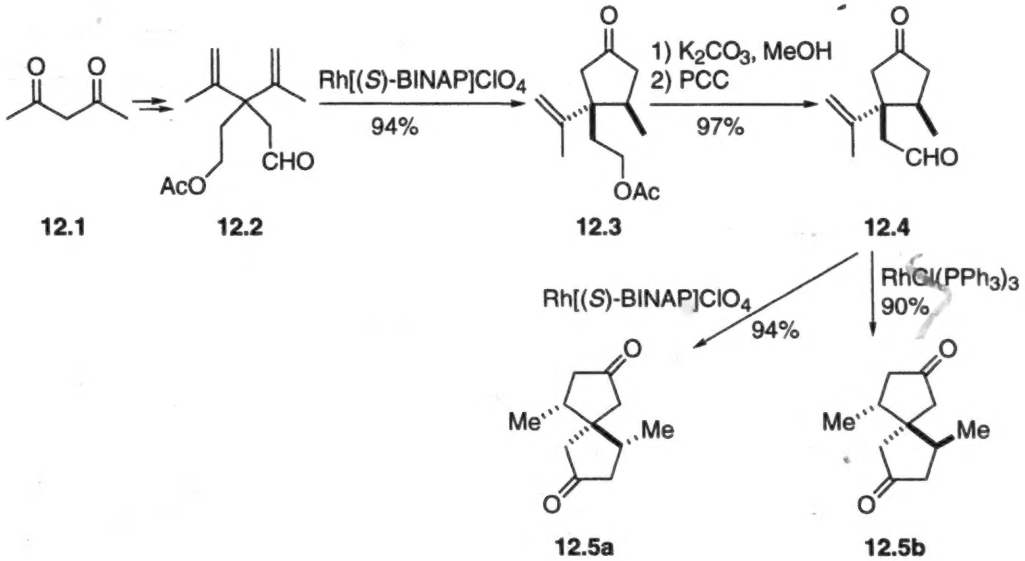


R2
COCl
COCl
R1
CH2N2
70-80%
N2
H
H
N2
5 mol%
Rh2(OAc)4
O
11.1
11.2a R1 = R2 = R3 = H
11.2b R1 = R2 = Me, R3 = H
11.2c R1 = Me, R2 = R3 = H
11.3
11.4a 27%
11.4b 35%
11.4c 35%
5 mol% Rh2(OAc)4
n = 1, 44%
n = 2, 44%
n = 3, 43%
n
11.5
11.7
CO2Et
5 mol% Rh2(OAc)4
n = 1, 43%
n = 2, 45%
n = 3, 41%
11.6
11.8

Scheme 11

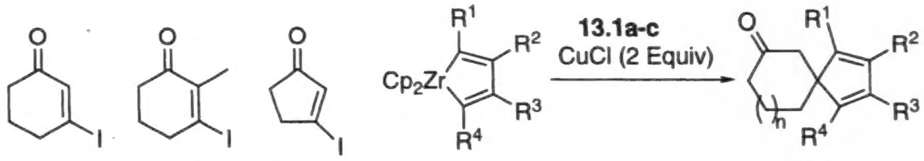
(Scheme 11). Acid chlorides (**11.1**) reacted with CH_2N_2 in Et_2O to give the α,α'-diazodicarbonyl derivatives **11.2**. Dirhodium tetraacetrate-catalyzed intramolecular C-H insertion gave spiranes **11.4**, presumably via **11.3**. Spiroannulation could also be effected from diketones **11.5** and **11.6** by the action of $Rh_2(OAc)_4$ to give **11.7** and **11.8**, respectively.

Tanaka[13] developed an asymmetric synthesis of spirodiketones using two successive Rh-catalyzed cyclizations. The substrate **12.2** was prepared from acetylacetone **12.1**. The first Rh[(*S*)-BINAP]ClO_4 catalyzed cyclization afforded **12.3**, which was converted into aldehyde **12.4**, and this was subjected to the second Rh-catalyzed cyclization. The spirocycles **12.5a** and **12.5b** were obtained by use of Rh[(*S*)-BINAP]ClO_4 and $RhCl(PPh_3)_3$, respectively.



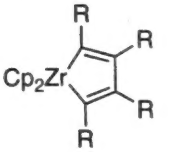
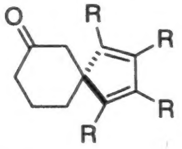
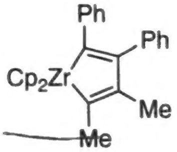
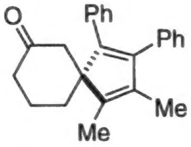
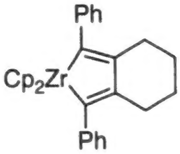
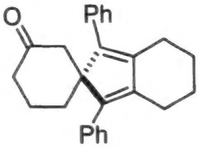
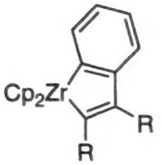
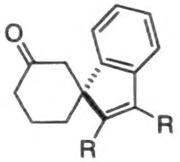
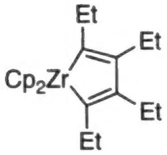
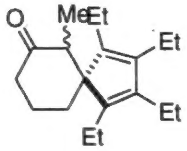
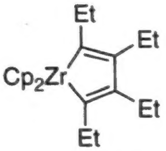
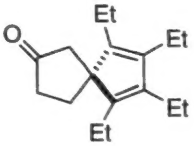
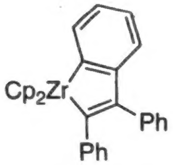
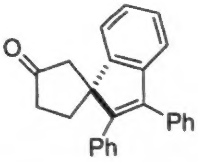
Rh[(S)-BINAP]ClO4
94%
1) K2CO3, MeOH
2) PCC
97%
CHO
AcO
OAc
Rh[(S)-BINAP]ClO4
94%
RhCl(PPh3)3
90%
Me
Me
12.1
12.2
12.3
12.4
12.5a
12.5b

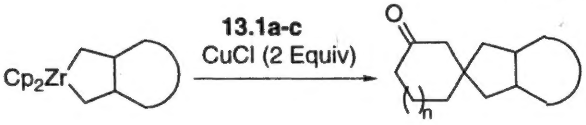
Scheme 12


O
I
Cp2Zr
R1
R2
R3
R4
13.1a-c
CuCl (2 Equiv)
n

13.1a **13.1b** **13.1c** **13.2** **13.3**

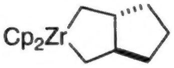
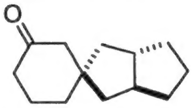
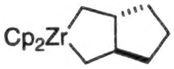
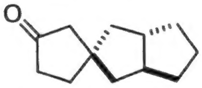
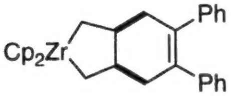
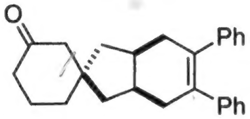
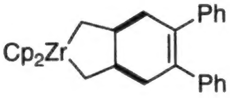
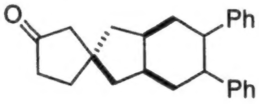
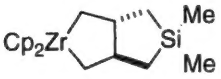
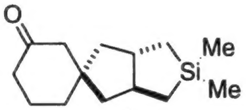
Table 3 Reaction of zirconacyclopentadiene with 3-iodocycloenones

Ziconacycle (**13.2**)	Enone (**13.1**)	Products (**13.3**)	Yield (%)
	**13.1a**		66 (R = Et) 78 (R = Ph)
	**13.1a**		48
	**13.1a**		48
	**13.1a**		56 (R = Et) 32 (R = Me)
	**13.1b**		42
	**13.1c**		78
	**13.1c**		61



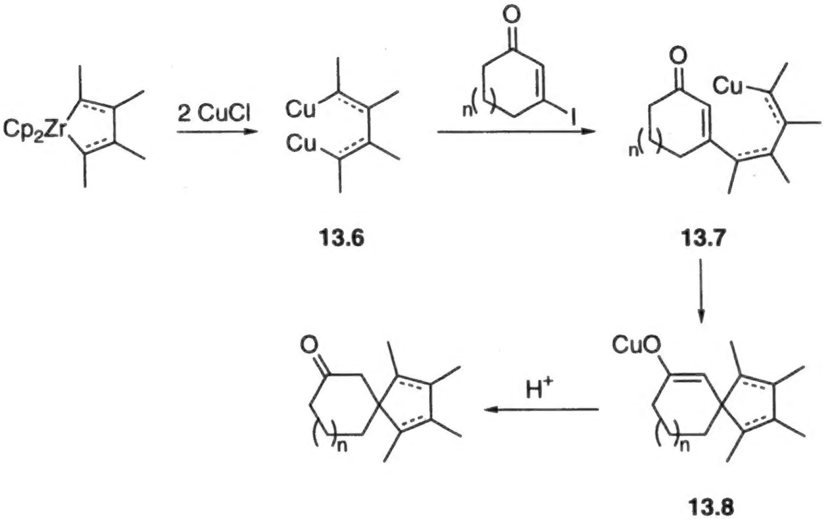
13.4 **13.5**

Table 4. Reaction of zirconacyclopentanes with 3-iodocycloenones

Ziconacycle (**13.2**)	Enone (**13.1**)	Products (**13.3**)	Yield (%)
	**13.1a**		80
	**13.1c**		69
	**13.1a**		56
	**13.1c**		50
	**13.1a**		41

d. Use of zirconacycles

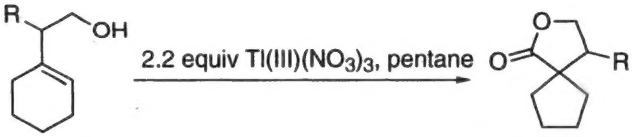
Takahashi[14] has used zirconacycles to form spirocyclic compounds by Michael addition and coupling in the presence of a stoichiometric amount of CuCl. The reaction of zirconacyclopentadiene **13.2** with 3-iodocycloalkenones **13.1** at room temperature in the presence of CuCl afforded spirocyclopentadienes **13.3** in moderate to good yields (Table 3). Zirconacyclopentane **13.4** was used under the same reaction conditions with **13.1**, and the corresponding tricyclic spirocompounds **13.5** were produced (Table 4). The authors


Cp$_2$Zr
2 CuCl
Cu
Cu
13.6
O
n
I
O
Cu
n
13.7
CuO
n
13.8
H$^+$
O
n

Scheme 13

also proposed a mechanism for these transformations (Scheme 13). In the first step transmetallation of the Zr-C bond in the zirconacycle to a Cu-C bond affords bis(cuprate) **13.6** that further reacts via cross-coupling with the C-I bond of iodocycloakenone to give the open-chain intermediate **13.7**. Intermediate **13.7** undergoes intramolecular Michael reaction to generate spiroenolate **13.8** that, after hydrolysis, affords a spirocylic compound.

e. Use of thallium salts


R
OH
2.2 equiv Tl(III)(NO$_3$)$_3$, pentane
O
O
R

14.1a, R = H
14.1b, R = Me

14.2a, R = H , 60%
14.2b, R = Me, 63%

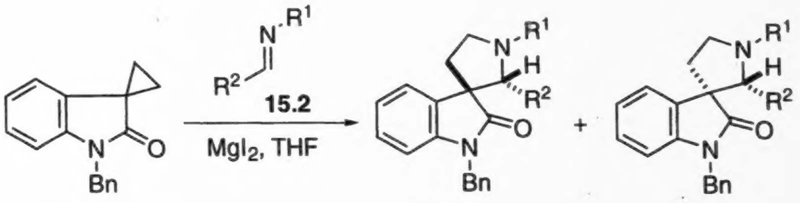
Scheme 14

Feffaz[15] used $Tl(NO_3)_3$ mediated ring contraction of cyclic homoallylic alcohols to make spirocycles. The reactions of the substrates **14.1a** and **14.1b** with 2.2 equiv of $Tl(NO_3)_3$ in pentane led to the spirolactones **14.2a** and **14.2b**, respectively (Scheme 14).

1.3 Rearrangement methods

a. Ring expansion of cyclopropanes

Carreira[16] reported an approach to the construction of the spiro[pyrrolidin-3,3'-oxindole] ring system (**15.3** and its

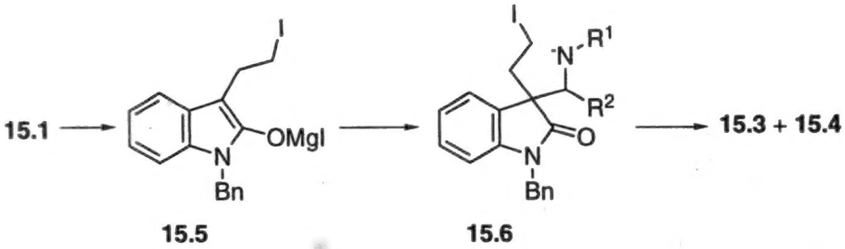


15.1 **15.3** **15.4**

Table 5. Reacction of spiro[cyclopropan-1,3'-oxindole] with aldimines

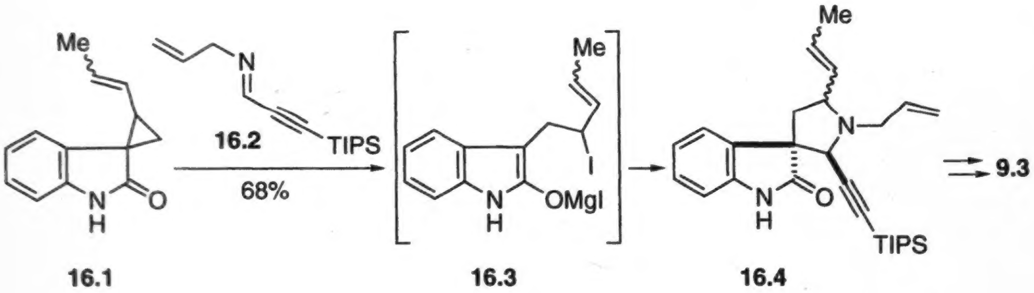
R^1	R^2	Yield (%)	**15.3:15.4**
$-CH_2CH_2CH_2CH_2-$		68	86:14
Allyl	Et	55	91:9
Allyl	*i*-Pr	83	80:20
Allyl	Ph	99	79:21
Bu	Ph	97	81:19
p-$TolSO_2$	Ph	97	91:9
p-$TolSO_2$	2-Me-C_6H_4	89	98:2
p-$TolSO_2$	4-Me-C_6H_4	96	64:36
p-$TolSO_2$	2-Br-C_6H_4	82	98:2
p-$TolSO_2$	4-Br-C_6H_4	92	82:18
p-$TolSO_2$	4-CF_3-C_6H_4	97	84:16
p-$TolSO_2$	4-OMe-C_6H_4	75	67:33
p-$TolSO_2$	2-Furyl	97	85:15
p-$TolSO_2$	PhCH=CH	62	74:26
p-$TolSO_2$	PhCH=C(Me)	55	52:48
p-$TolSO_2$	*i*-Pr_3SiCCH	77	98:2

C-3 epimer **15.4**) by reaction of spiro[cyclopropan-1,3'-oxindole] **15.1** and aldimines **15.2** with good diastereoselectivity (Table 5). A mechanistic pathway was proposed. Iodide effects ring opening of the cyclopropane **15.1**, furnishing enolate **15.5**, and reaction of **15.5** with the starting imine **15.2** gives **15.6**, which can undergo alkylative cyclization to produce **15.3** and **15.4** (Scheme 15).


15.1
OMgI
N
Bn
15.5
I
N
R1
R2
O
N
Bn
15.6
15.3 + 15.4

Scheme 15

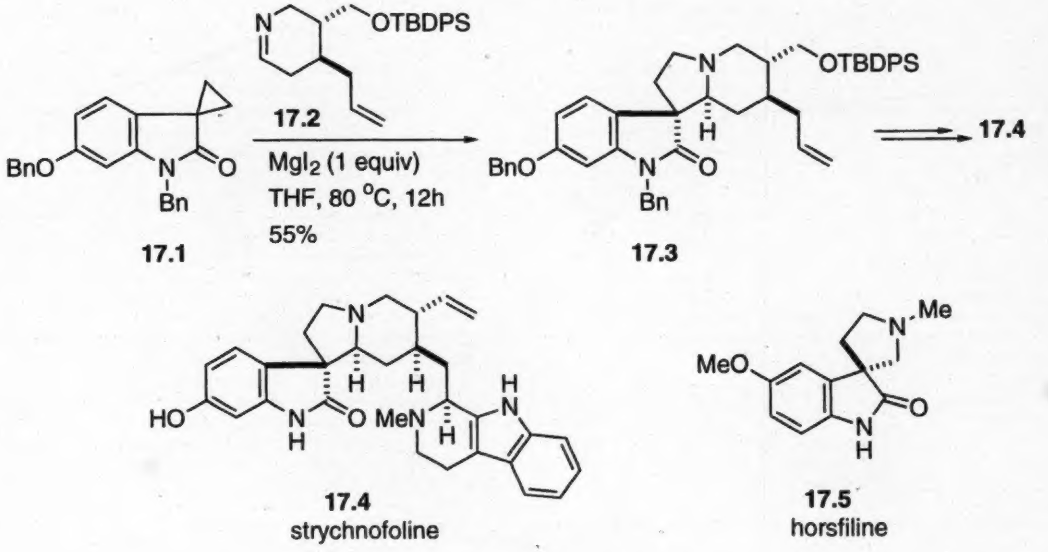
In their total synthesis of (-)-spirotryprostatin B, Meyers and Carreira[17] used the MgI_2-catalyzed ring expansion as the key reaction. When a solution of cyclopropane **16.1** and imine **16.2** was heated in THF at 75 °C in a sealed tube in the presence of 1 equiv of MgI_2, spirolactam **16.4** was isolated in 68% yield via **16.3**. The product was isolated as


Me
N
H
O
16.1
N
16.2
TIPS
68%
Me
I
N
H
OMgI
16.3
Me
N
N
H
O
TIPS
16.4
9.3

Scheme 16

a 6:1 mixture of diastereoisomers favoring the desired relative stereochemistry found in the natural product, and the major diastereoisomer was converted efficiently into (-)-spirotryprostatin B (**9.3**) (Scheme 16).

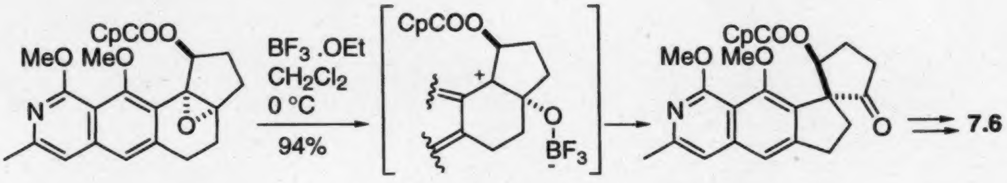
Lerchner and Carreira[18] applied the same method of making spirolactams by ring expansion in the synthesis of (±)-strychnofoline (**17.4**). The spirocyclic compound **17.3** was prepared from cyclopropane **17.1** and imine **17.2** in the presence of MgI_2. Compound **17.3** was then converted into strychnofoline (**17.4**) by a multistep transformation (Scheme 17). The same group[19] also achieved the synthesis of (±)-horsfiline (**17.5**) by the same strategy.


OTBDPS
17.2
MgI2 (1 equiv)
THF, 80 °C, 12h
55%
BnO
Bn
17.1
OTBDPS
BnO
Bn
17.3
17.4
HO
MeN
17.4
strychnofoline
MeO
Me
17.5
horsfiline

Scheme 17

b. Epoxide rearrangement

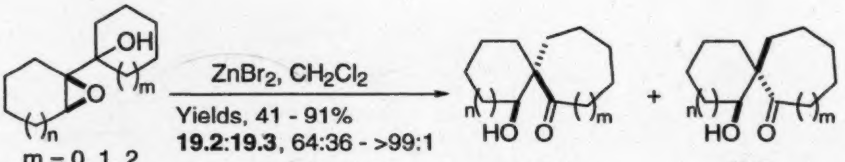
During a study of the enantioselective total synthesis of fredericamycin A (**7.6**), Kita[20] used a stereospecific rearrangement of optically active benzo-fused epoxy acylates to make spirocyclic systems. The *trans*-epoxy camphanate (-)-**18.1** (≥99% de) was treated with $BF_3 \cdot OEt_2$ at 0 °C to give the optically pure spirocompound (+)-**18.3** (≥99% de in 94% yield), via intermediate **18.2**. Compound **18.3** was transformed stereospecifically into fredericamycin A (**7.6**, 97% ee) by a multistep sequence (Scheme 18).


CpCOO
MeO MeO
N
O
BF3 .OEt
CH2Cl2
0 °C
94%
CpCOO
+
O
BF3
-
CpCOO
MeO MeO
N
O
7.6

(-)-18.1 **18.2** **(+)-18.3**

Scheme 18

Zinc bromide had proved to be an efficient catalyst for the stereoselective semipinacol rearrangement of α-hydroxy epoxides as reported by Tu *et al.*[21] The α-hydoxyepoxides with five- or six-membered rings (**19.1**) were selected for investigation, and compounds **19.2** were isolated as the major products (Scheme 19).

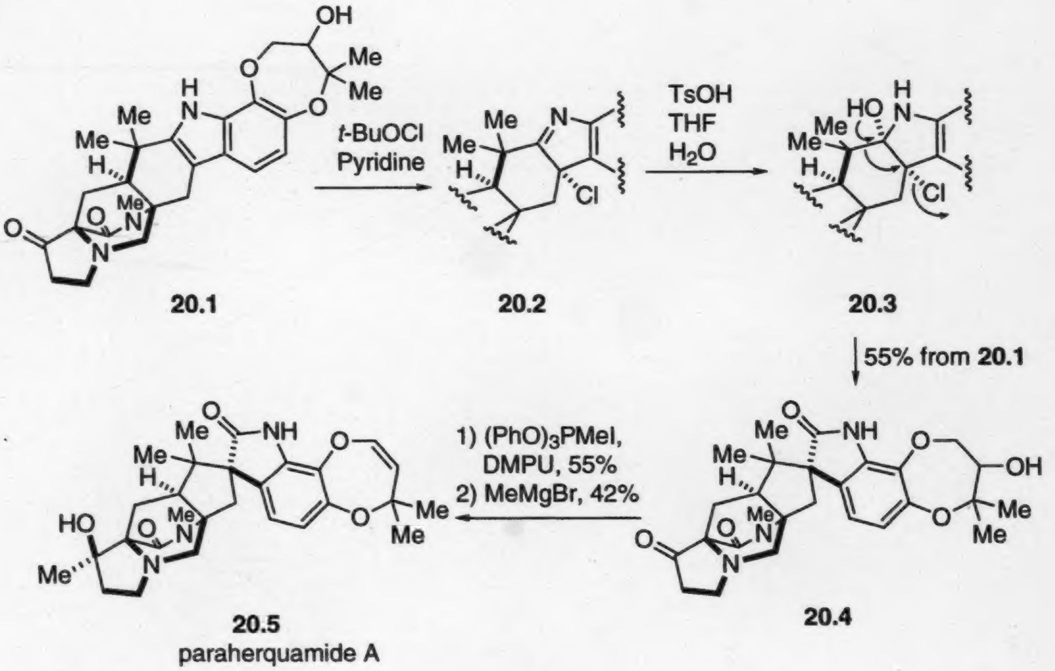

OH
O
m
n
ZnBr2, CH2Cl2
Yields, 41 - 91%
19.2:19.3, 64:36 - >99:1
n
HO
O
m
+
n
HO
O
m

m = 0, 1, 2
n = 0, 1
19.1 **19.2** **19.3**

Scheme 19

c. *Pinacol and related rearrangements*

In Williams' total synthesis of paraherquamide A (**20.5**),[22] a pinacol-type rearrangement was used to construct the spirocenter. Chlorination of **20.1** with *t*-BuOCl in pyridine provided a labile 3-chloroindolenine (**20.2**). The pinacol-type rearrangement was conducted by treating **20.2** with *p*-TsOH.H_2O in THF-water, and the desired spirooxindole **20.4** was produced stereospecifically. Dehydration, followed by methyl Grignard addition gave paraherquamide A (**20.5**) (Scheme 20).

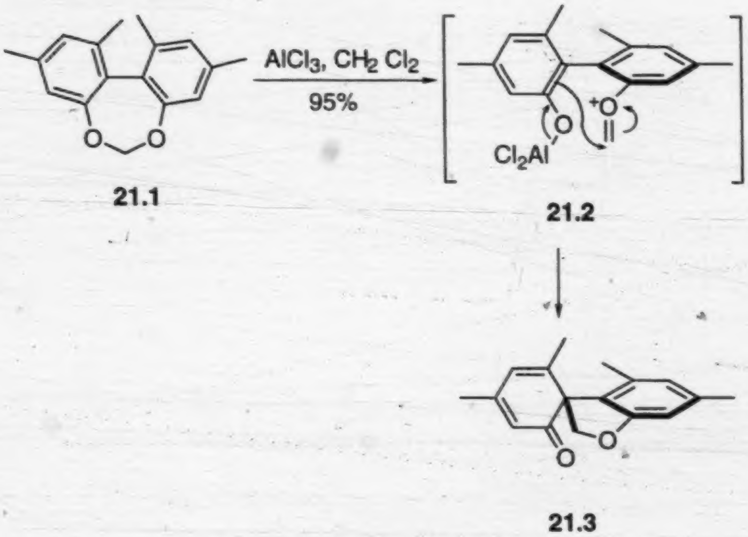


OH
Me
Me
H
N
O
O
Me
Me
H
O
O
Me
N
N
t-BuOCl
Pyridine
N
Cl
TsOH
THF
H2O
HO
H
N
Cl
20.1
20.2
20.3
55% from 20.1
NH
OH
1) (PhO)3PMeI, DMPU, 55%
2) MeMgBr, 42%
HO
Me
20.5
paraherquamide A
20.4

Scheme 20

d. *C-Alkylation of phenolic precursors*

Coleman[23] reported an unusual intramolecular *C*-alkylation of a phenolate. Dibenzodioxepin **21.1** was treated with $AlCl_3$ in CH_2Cl_2, and the spirocyclic product **21.3** was formed by acetal cleavage, followed by *C*-alkylation (Scheme 21). However, this reaction seems not to be general since corresponding reactions did not work even if the only structural change were removal of the methyl substituents in the starting compound.

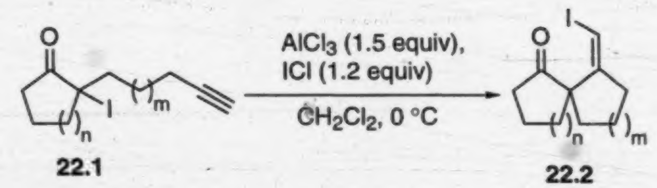


Scheme 21

e. *Ionic iodo-carbocyclization*

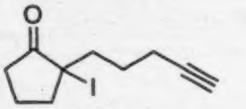
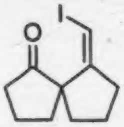
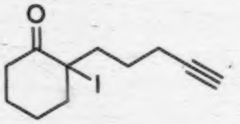
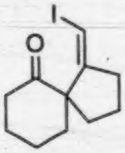
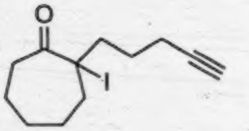
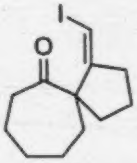
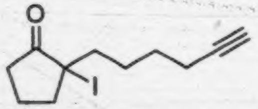
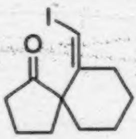
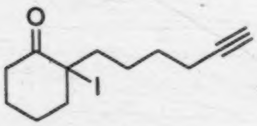
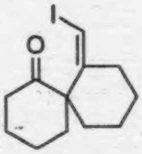
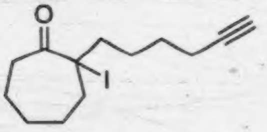
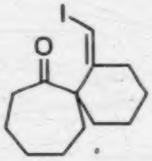
Sha[24] investigated $AlCl_3$/ICl mediated iodocarbocyclization of α-iodocycloalkanones to make spirocylic ketones (**22.1** → **22.2**). The results are summarized in Table 6. The author also proposed a mechanism for this transformation (Scheme 22). The $AlCl_3$ reacts with the α-iodoketone to generate an aluminum enolate and ICl. The acetylenic moiety on the side chain then complexes with ICl to give intermediate **22.4**. Cyclization of **22.4** would afford

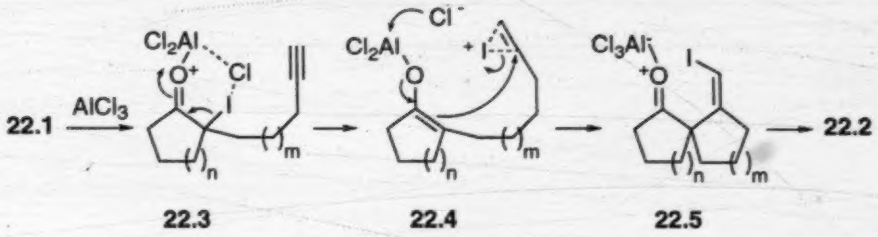
$AlCl_3$-complex **22.5**. Upon aqueous work-up, complex **22.5** is hydrolyzed to spiroketone **22.2**.


AlCl3 (1.5 equiv),
ICl (1.2 equiv)
CH2Cl2, 0 °C
n
m

22.1 **22.2**

Table 6. Ionic iodocarbocyclization

Cycloalkanone	Product	Yield (%)
		83
		81
		70
		94
		74
		77

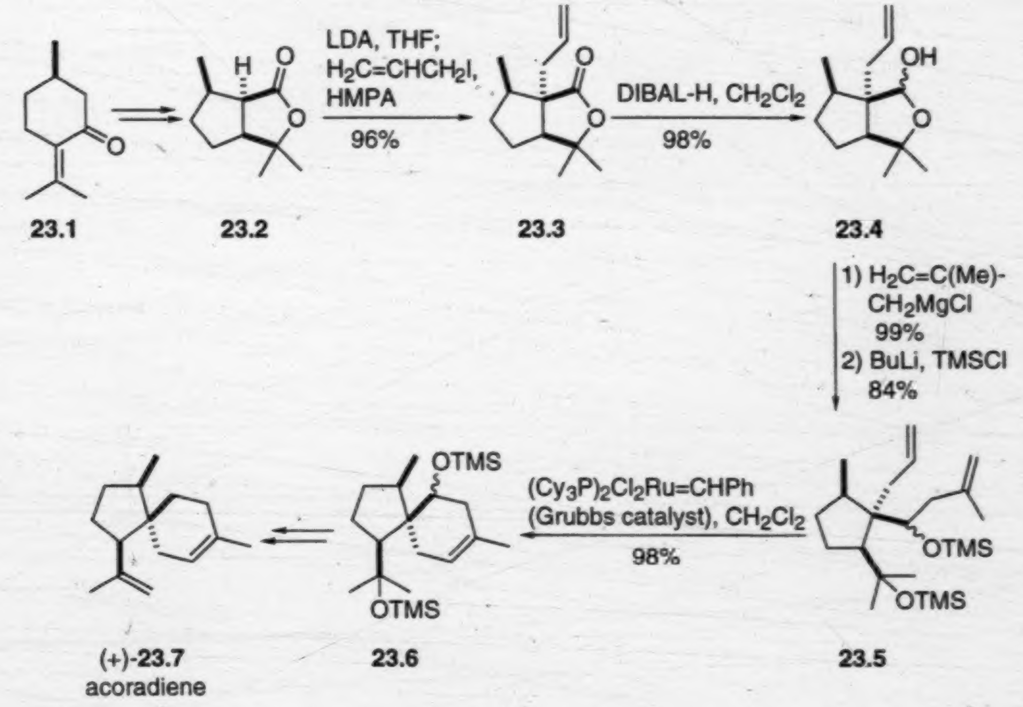


Scheme 22

1.4 Ring closure of geminally disubstituted cyclic systems

a. Use of Grubbs' catalyst

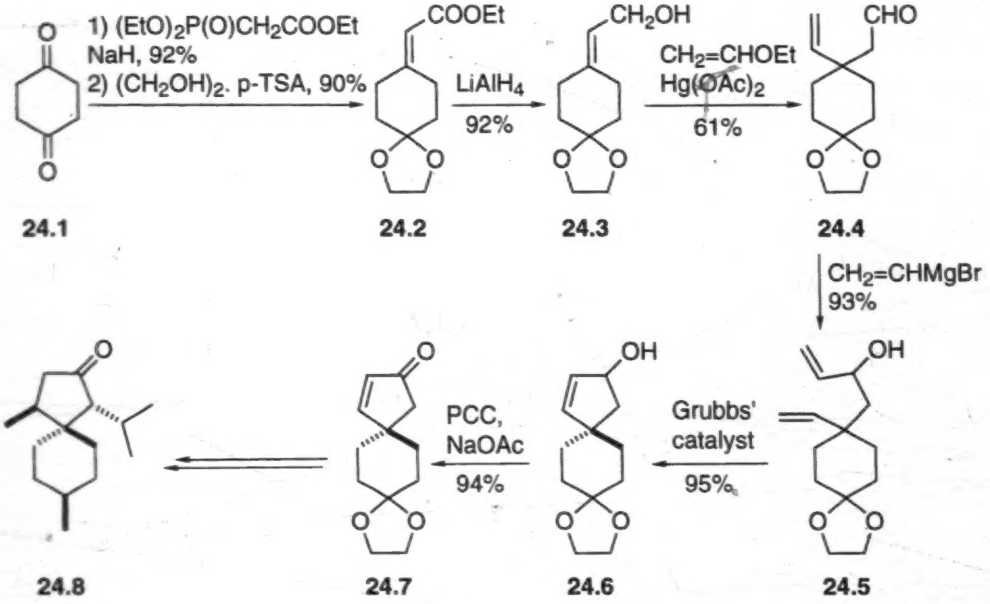
Mori[25] synthesized (1*R*,4*R*,5*S*)-(+)-acoradiene (**23.7**) starting from readily available (*R*)-(+)-pulegone (**23.1**). Alkylation of **23.2** set up the quaternary center. Ring-



Scheme 23

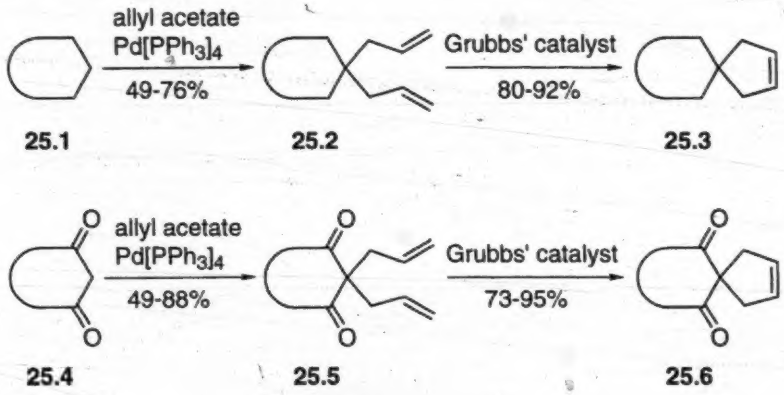
closing olefin metathesis of **23.5** by Grubbs catalyst afforded spirocycle **23.6** as a diastereoisomeric mixture, and this can be further transformed into (1*R*,4*R*,5*S*)-(+)-acoradiene (**23.7**) (Scheme 23).

In a formal synthesis of (±)-acorones, Srikrishna[26] applied a ring closing metathesis approach for the spiroannulation. The quaternary carbon of **24.4** was introduced via Claisen rearrangement of the allyl alcohol **24.3**. Ring closing metathesis (**24.5** → **24.6**), catalyzed by Grubbs' catalyst, served as the main transformation in the route to the spiroketone **24.7** (Scheme 24); this compound had previously been transformed into (±)-acorone.[27] A number of other spirocycles were prepared by a similar reaction sequence.


1) $(EtO)_2P(O)CH_2COOEt$
NaH, 92%
2) $(CH_2OH)_2$. p-TSA, 90%
COOEt
$LiAlH_4$
92%
CH_2OH
CH_2=CHOEt
$Hg(OAc)_2$
61%
CHO
24.1
24.2
24.3
24.4
CH_2=CHMgBr
93%
OH
Grubbs' catalyst
95%
PCC, NaOAc
94%
24.8
24.7
24.6
24.5

Scheme 24

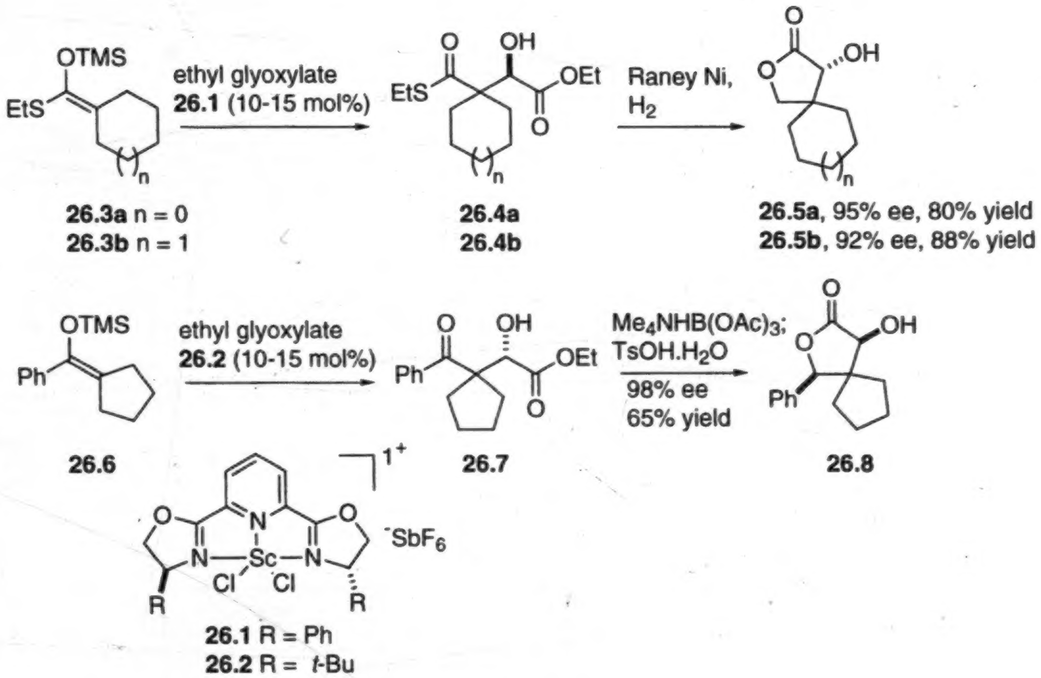
Kotha[28] made a number of spirocylic compounds by palladium catalyzed allylation of both active methylene substrates (**25.1**) and β-dicarbonyl compounds (**25.4**), followed by ring-closing metathesis. Spirocyclic alkenes **25.3** and **25.6** were prepared by this route (Scheme 25).


allyl acetate
Pd[PPh3]4
49-76%
Grubbs' catalyst
80-92%
25.1
25.2
25.3
allyl acetate
Pd[PPh3]4
49-88%
Grubbs' catalyst
73-95%
25.4
25.5
25.6

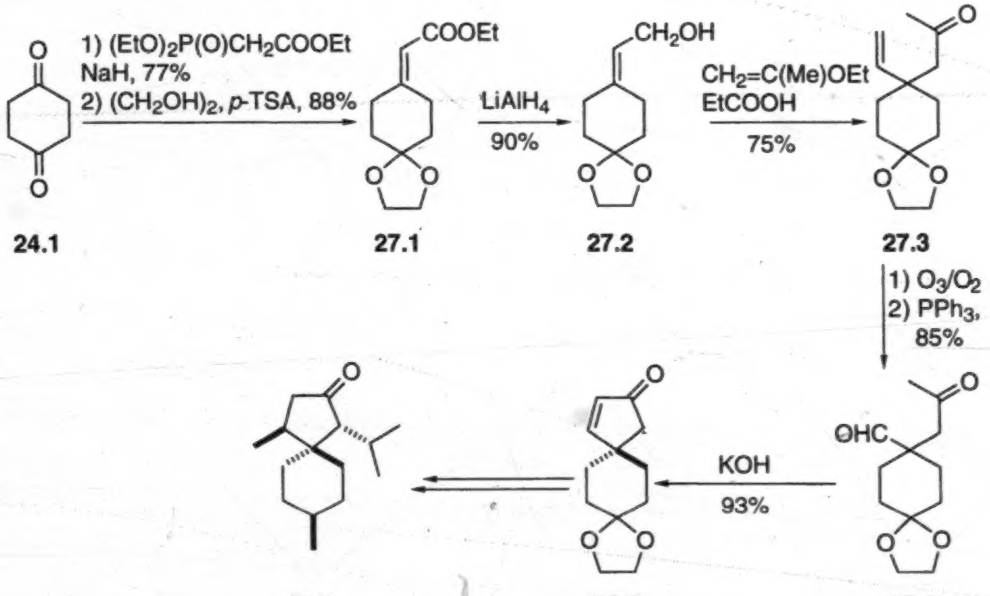
Scheme 25

b. Alkylation and reductive ring closure

Evans[29] used Sc catalysts **26.1** and **26.2** to mediate the aldol reaction between thiosilylketene acetals **26.3a,b** and enolsilane **26.6** with ethyl glyoxylate to give aldol adducts **26.4a,b** and **26.7** respectively. Hydrogenation of the thioesters **26.4a,b** to the derived primary alcohol and spontaneous lactonization afforded the spirolactones **26.5a,b** in very good yield and enantioselectivity. *Anti* reduction of hydroxyester **26.7** with $Me_4NHB(OAc)_3$, followed by treatment with catalytic *p*-TsOH.H_2O, gave **26.8** in 98% ee (Scheme 26).


OTMS
EtS
n
ethyl glyoxylate
26.1 (10-15 mol%)
O
OH
EtS
OEt
O
n
Raney Ni, H_2
O
O
OH
n
26.3a n = 0
26.3b n = 1
26.4a
26.4b
26.5a, 95% ee, 80% yield
26.5b, 92% ee, 88% yield
OTMS
Ph
ethyl glyoxylate
26.2 (10-15 mol%)
O
OH
Ph
OEt
O
$Me_4NHB(OAc)_3$;
$TsOH.H_2O$
98% ee
65% yield
O
O
OH
Ph
26.6
26.7
26.8
1^+
N
O
O
N
Sc
N
Cl
Cl
$^-SbF_6$
R
R
26.1 R = Ph
26.2 R = t-Bu

Scheme 26


O
O
1) $(EtO)_2P(O)CH_2COOEt$
NaH, 77%
2) $(CH_2OH)_2$, p-TSA, 88%
COOEt
O O
LiAlH$_4$
90%
CH_2OH
O O
$CH_2=C(Me)OEt$
EtCOOH
75%
O
O O
24.1
27.1
27.2
27.3
1) O_3/O_2
2) PPh_3,
85%
O
OHC
O O
KOH
93%
O
O O
O
24.8
24.7
27.4

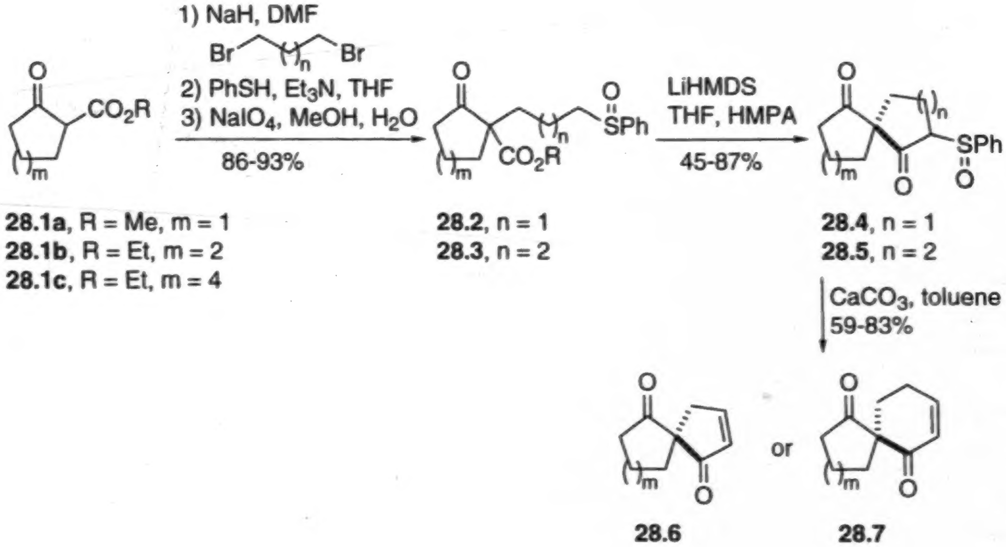
Scheme 27

c. Alkylation and intramolecular aldol condensation

In their formal synthesis of (±)-acorone[27] (**24.8**), Srikrishna and Kumar used a Claisen rearrangement to make the quaternary center (**27.2** → **27.3**). Intramolecular aldol condensation of ketoaldehyde **27.4** with 1 N methanolic KOH in THF furnished the spiroenone **24.7**, a compound which had previously been transformed into (±)-acorone[27b,c] (Scheme 27).

d. Intramolecular acylation of α-sulfinyl carbanions

Starting from readily available cyclic β-ketoesters **28.1a-c**,[30] the sulfoxides **28.2** and **28.3** could be obtained in good overall yields. The spirodiones **28.4** and **28.5** were then prepared by intramolecular acylation. Sulfoxide elimination, with generation of a double bond, could be achieved by refluxing in PhMe in the presence of $CaCO_3$ (Scheme 28).



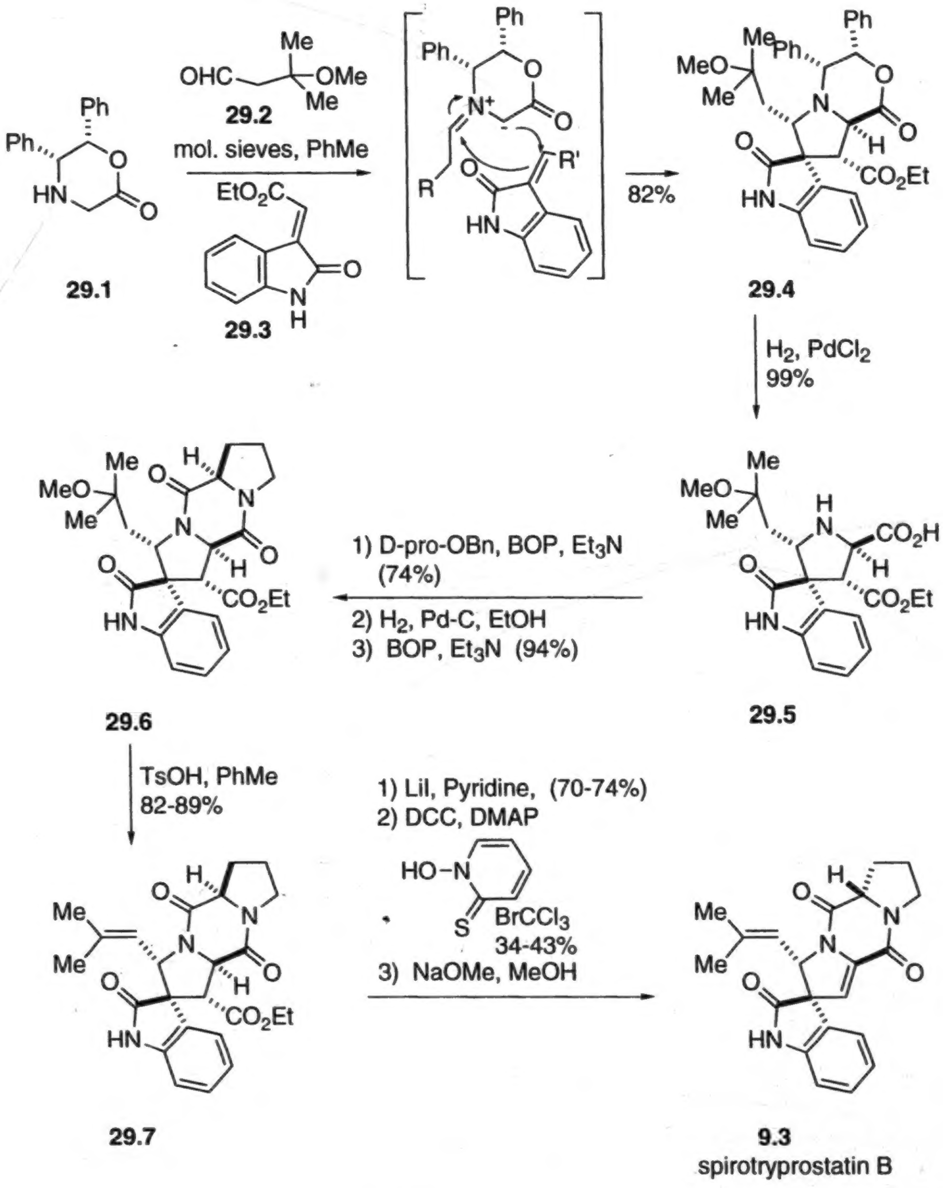
1) NaH, DMF
Br, Br, n
2) PhSH, Et3N, THF
3) NaIO4, MeOH, H2O
86-93%
CO2R
m
SPh
LiHMDS
THF, HMPA
45-87%
28.1a, R = Me, m = 1
28.1b, R = Et, m = 2
28.1c, R = Et, m = 4
28.2, n = 1
28.3, n = 2
28.4, n = 1
28.5, n = 2
CaCO3, toluene
59-83%
or
28.6
28.7

Scheme 28

1.5 Cycloaddition methods

a. *[3+2] Cycloaddition*

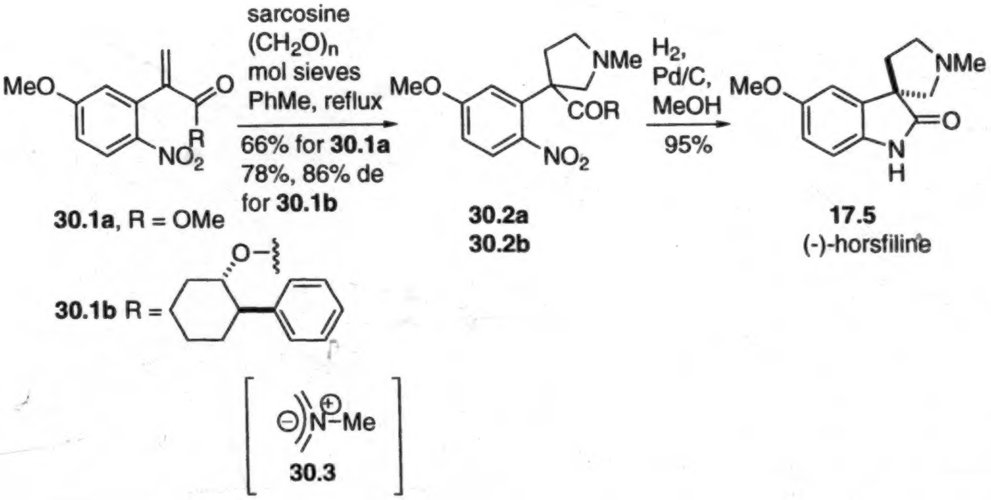
In Williams' asymmetric total synthesis[31] of (+)- and (-)-spirotryprostatin B (**9.3**), an asymmetric [1,3]-dipolar


29.1
29.2
mol. sieves, PhMe
29.3
82%
29.4
H2, PdCl2
99%
1) D-pro-OBn, BOP, Et3N (74%)
2) H2, Pd-C, EtOH
3) BOP, Et3N (94%)
29.5
29.6
TsOH, PhMe
82-89%
1) LiI, Pyridine, (70-74%)
2) DCC, DMAP
BrCCl3
34-43%
3) NaOMe, MeOH
29.7
9.3
spirotryprostatin B

Scheme 29

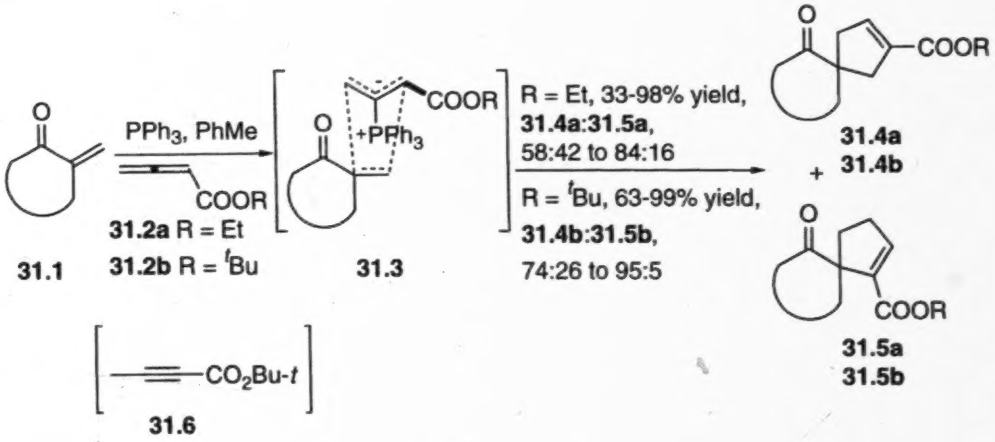
cycloaddition was applied to set up the spirocenter. The reaction of oxazinone **29.1** with aldehyde **29.2** and oxindole **29.3** in PhMe at room temperature in the presence of 3 Å molecular sieves afforded **29.4**. This reaction, which sets up four contiguous stereogenic centers, constructs the entire prenylated tryptophyl moiety of spirotryprostatin B in a single, simple operation. The synthesis of spirotryprostatin B was completed by a very short sequence (Scheme 29).

Palmisano[32] applied a similar strategy in the asymmetric synthesis of (-)-horsfiline (**17.5**). Dipolarophile **30.1a** reacted with the putative *N*-methylazomethine ylide **30.3** from sarcosine (*N*-methylglycine), and hydrogenation, followed by spontaneous lactamization, afforded racemic **17.5**. The enantioselective synthesis could be achieved by a similar reaction sequence, by changing only the methyl ester **30.1a** to a chiral moiety attached ester **30.1b** (Scheme 30).


MeO
O
R
NO_2
30.1a, R = OMe
30.1b R =
O
sarcosine
$(CH_2O)_n$
mol sieves
PhMe, reflux
66% for 30.1a
78%, 86% de
for 30.1b
MeO
NMe
COR
NO_2
30.2a
30.2b
H_2,
Pd/C,
MeOH
95%
MeO
NMe
O
N
H
17.5
(-)-horsfiline
N–Me
30.3

Scheme 30

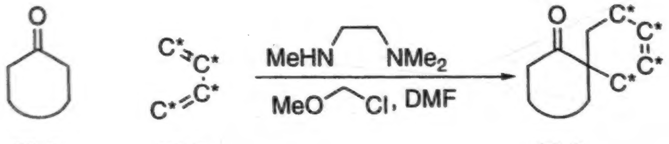
Lu[33] used a phosphine-catalyzed [3+2] cycloaddition for the regioselective construction of spirocycles. *Exo*-methylenecycles **31.1** were used as the dipolarophile, and 2,3-butadienoate **31.2** with Ph_3P served as the 1,3-dipole. When the *t*-butyl ester was used, the reactions were much improved in both yields and selectivities, and the reaction favored **31.4** via transition state **31.3** (Scheme 31). When acetylene **31.6** was used instead of **31.2b**, the reactions also preceded with good selectivities (89:11 to 97:3).


O
PPh3, PhMe
COOR
31.2a R = Et
31.2b R = tBu
31.1
O
+PPh3
COOR
31.3
R = Et, 33-98% yield,
31.4a:31.5a,
58:42 to 84:16
R = tBu, 63-99% yield,
31.4b:31.5b,
74:26 to 95:5
O
COOR
31.4a
31.4b
+
O
COOR
31.5a
31.5b
CO2Bu-t
31.6

Scheme 31

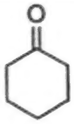
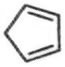
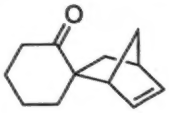
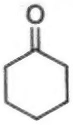
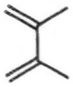
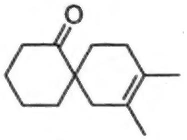
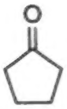
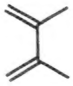
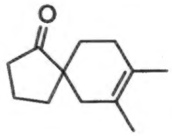
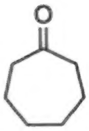
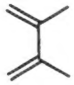
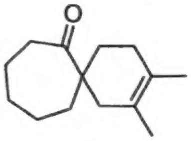
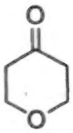
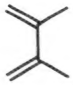
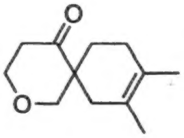
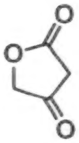
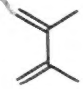
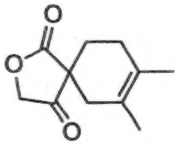
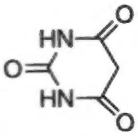
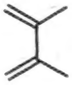
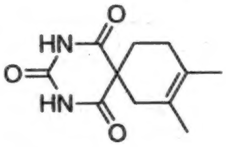
b. Intermolecular Diels-Alder reaction

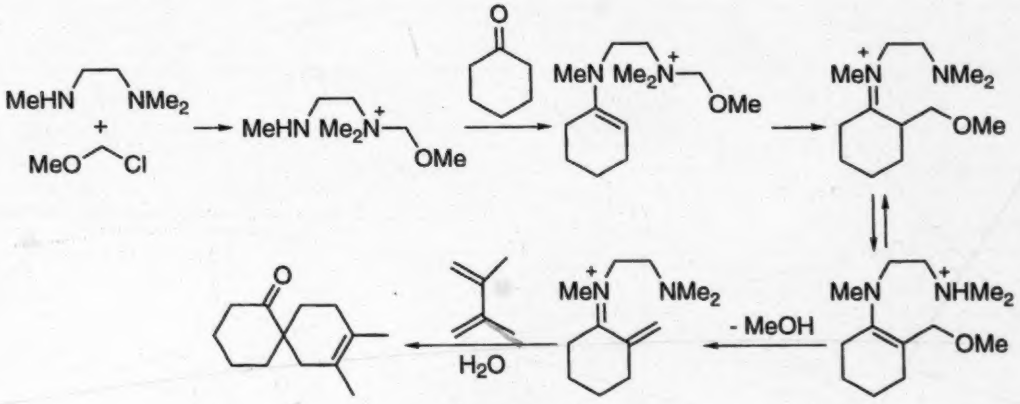
A one-pot synthesis of spiroalkanones from cycloalkanones and dienes promoted by an ammonium salt was described by Yamamoto.[34] The reaction proceeds through a tandem α-methylenation/Diels-Alder process. A number of ketones (**32.1**) reacted with various dienes **32.2** in the presence of *N,N,N'*-trimethylethylenediamine and $MeOCH_2Cl$ in DMF to produce spirocycles **32.3** (Table 7). A possible mechanism represented by cyclohexanone and isoprene was proposed as shown in Scheme 32.



32.1 **32.2** **32.3**

Table 7. Tandem α-methylenation/Diels-Alder reaction to make spirocycles

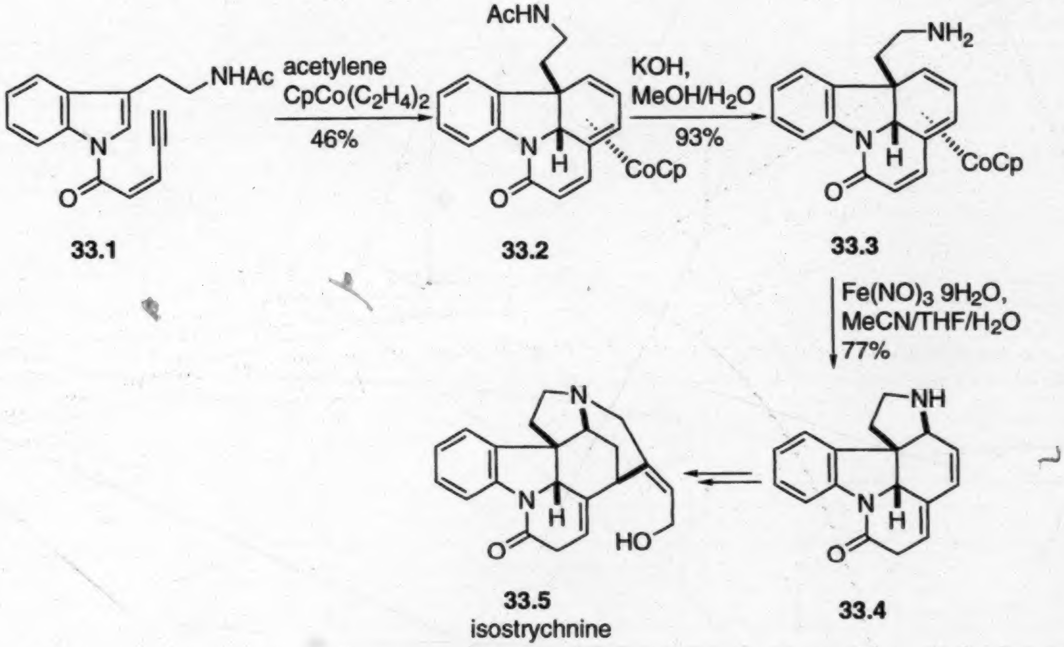
Ketone	Diene	Product	Yield (%)
			52
			78
			33
			57
			65
			75
			91


MeHN
NMe$_2$
MeO
Cl
MeHN Me$_2$N$^+$
OMe
MeN Me$_2$N$^+$
MeN$^+$
NMe$_2$
OMe
MeN
NHMe$_2^+$
OMe
- MeOH
H$_2$O

Scheme 32

c. [2+2+2] Cycloaddition

Vollhardt[35] used a cobalt-mediated cycloaddition in his approaches to the synthesis of (±)-isostrychnine. Cobalt-

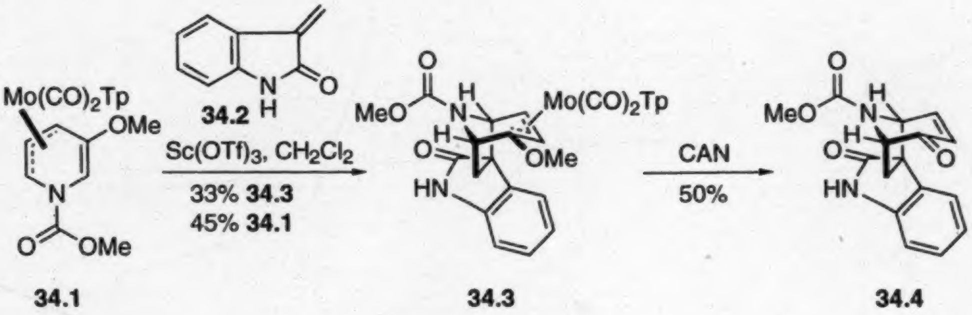

NHAc
acetylene
CpCo(C$_2$H$_4$)$_2$
46%
AcHN
CoCp
KOH,
MeOH/H$_2$O
93%
NH$_2$
CoCp
33.1
33.2
33.3
Fe(NO)$_3$ 9H$_2$O,
MeCN/THF/H$_2$O
77%
NH
HO
33.5
isostrychnine
33.4

Scheme 33

mediated [2+2+2] cyclization of enynoylindole **33.1** with acetylene in the presence of $CpCo(C_2H_4)_2$ gave the desired dihydrocarbazole complex **33.2** in 46% yield. Deacetylation, followed by demetallation using $Fe(NO)_3 \cdot 9H_2O$, gave intermediate **33.4** (Scheme 33), which was successfully transformed into the natural product **33.5**.

d. [5+2] Cycloaddition

Liebeskind[36] applied Mo-complex **34.1** in the synthesis of spirooxindole alkaloids based on the [5+2] cycloaddition. Reaction of **34.1** with methyleneoxindole **34.2** in the presence of the mild Lewis acid $Sc(OTf)_3$ provided the desired adduct **34.3**, which can be converted into the useful intermediate **34.4** by oxidative demetallation using CAN.

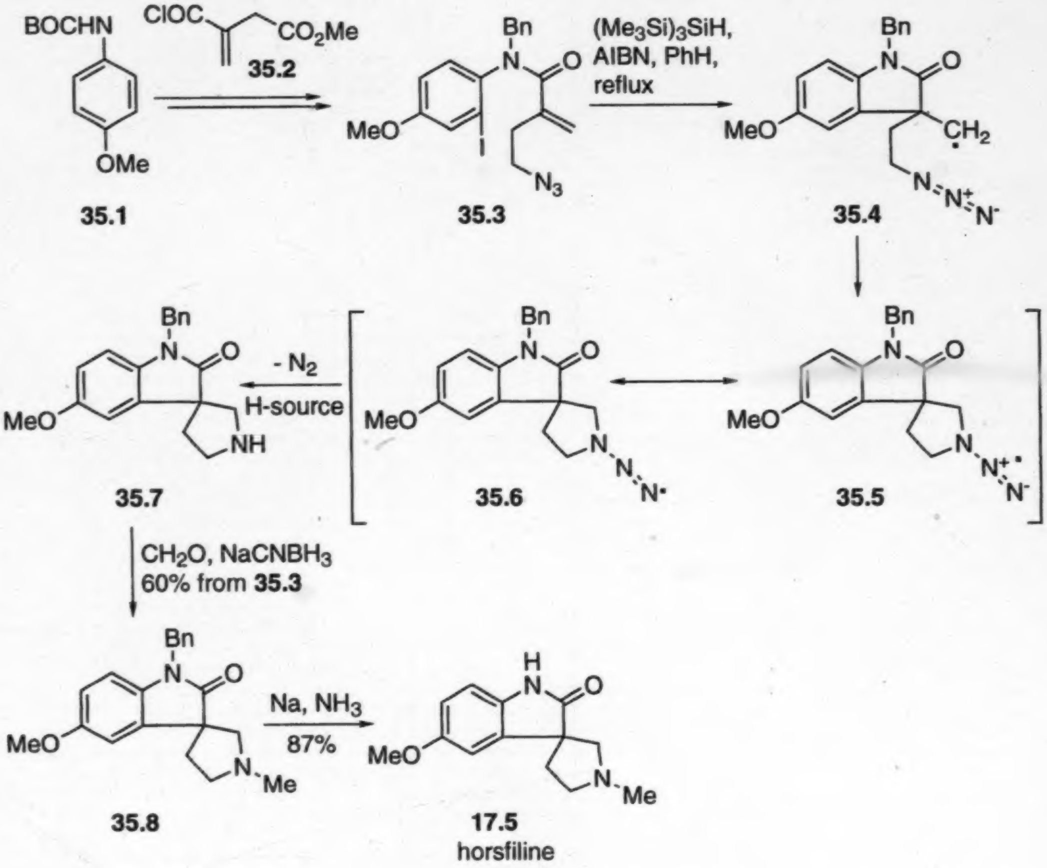

Mo(CO)2Tp
OMe
N
O
OMe
34.1
N
O
34.2 H
Sc(OTf)3, CH2Cl2
33% 34.3
45% 34.1
O
MeO
N
H
H
Mo(CO)2Tp
OMe
O
HN
34.3
CAN
50%
O
MeO
N
H
H
O
O
HN
34.4

Scheme 34

1.6 Radical cyclization methods

a. Tandem radical spirocyclization

In the synthesis of (±)-horsfiline, Murphy *et al.*[37] used a tandem radical cyclization strategy. The radical reaction precursor (**35.3**) was treated with $(Me_3Si)_3SiH$ and AIBN in refluxing PhH, and the spirolactam **35.7** was produced via a tandem 5-*exo*-trigonal radical processes (**35.3** → **35.4** → **35.5**), followed by loss of N_2. The natural product horsfiline (**17.5**) was then reached by an *in situ* methylation followed by debenzylation.

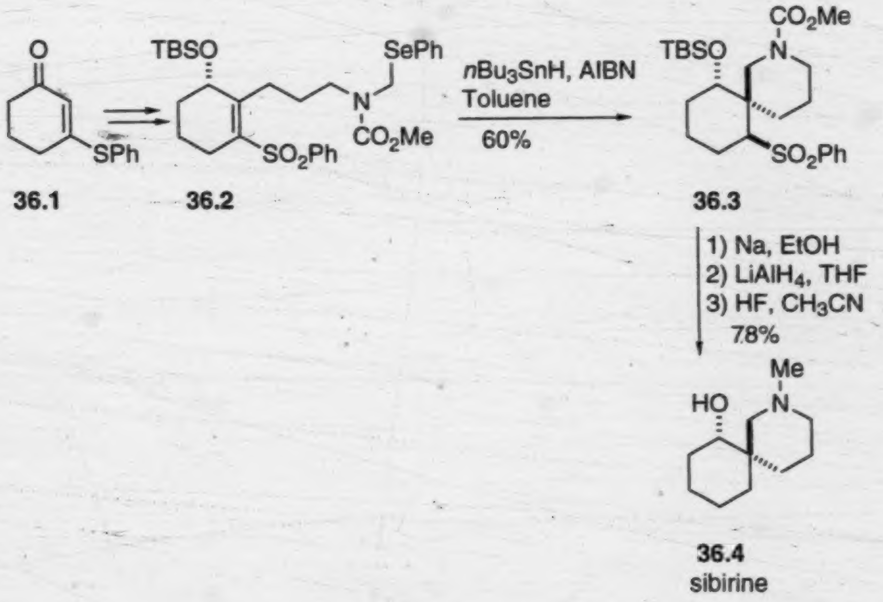

BOCHN
OMe
35.1
ClOC
CO2Me
35.2
Bn
N
O
MeO
I
N3
35.3
(Me3Si)3SiH,
AIBN, PhH,
reflux
Bn
N
O
MeO
CH2
N
N+
N-
35.4
Bn
N
O
MeO
N
N+
N-
35.5
Bn
N
O
MeO
N
N
N•
35.6
- N2
H-source
Bn
N
O
MeO
NH
35.7
CH2O, NaCNBH3
60% from 35.3
Bn
N
O
MeO
N
Me
35.8
Na, NH3
87%
H
N
O
MeO
N
Me
17.5
horsfiline

Scheme 35

b. Radical spirocyclization

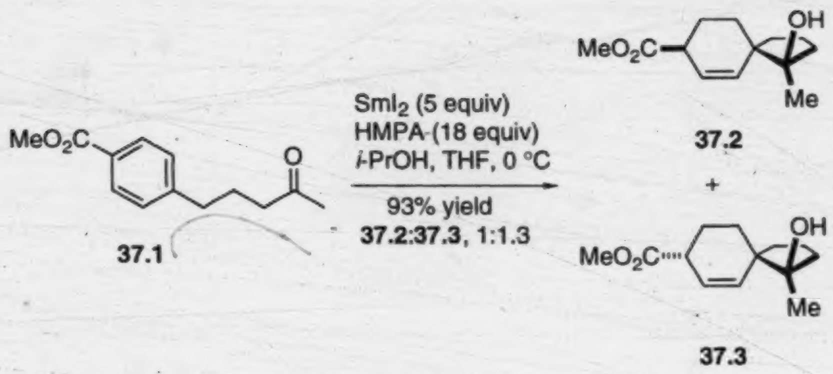
Koreeda[38] synthesized the spirocyclic alkaloid sibirine by using a radical cyclization as the key step. The sulfone-containing radical precursor **36.2**, which was made from 3-

phenylthio-2-cyclohexen-1-one (**36.1**), underwent 6-*exo*-trigonal cyclization with the radical center approaching from the opposite face to the $OSiMe_2Bu$-*t* group. This process gave the spirocycle **36.3** with the indicated stereochemistry. Sibirine (**36.4**) could then be prepared by a three step sequence in 78% overall yield for the three steps (Scheme 36).


O
SPh
36.1
TBSO
SePh
N
CO2Me
SO2Ph
36.2
nBu3SnH, AIBN
Toluene
60%
CO2Me
TBSO
N
SO2Ph
36.3
1) Na, EtOH
2) LiAlH4, THF
3) HF, CH3CN
78%
Me
HO
N
36.4
sibirine

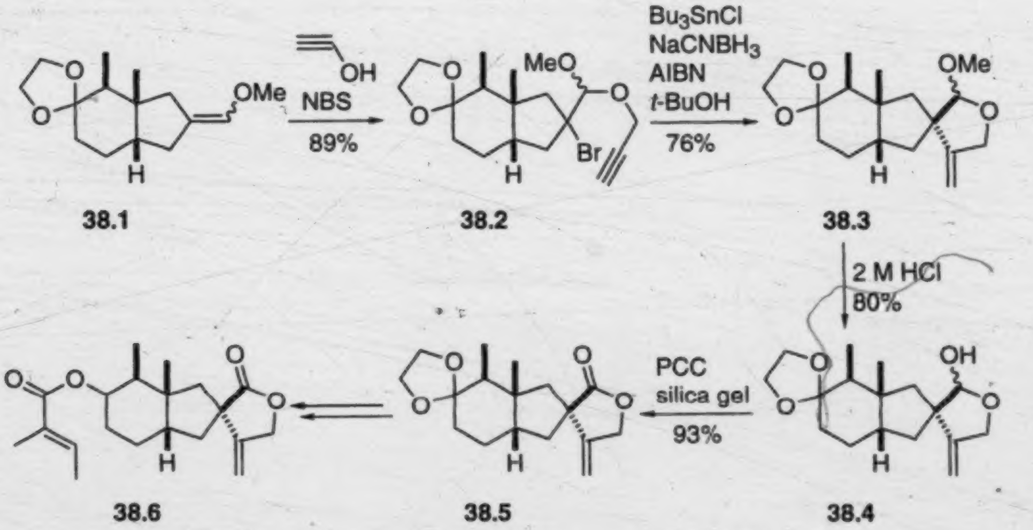
Scheme 36

The first samarium(II)-mediated stereoselective spirocyclization onto an aromatic ring was reported by Tanaka.[39] This was achieved by reaction of methyl 4-(4-oxopentyl)benzoate (**37.1**) with SmI_2 in the presence of *i*-PrOH and HMPA, and yielded spirocycles **37.2** and **37.3** stereoselectively. In this reaction SmI_2 served as both a radical source and a reducing reagent.


MeO$_2$C
O
37.1
SmI$_2$ (5 equiv)
HMPA (18 equiv)
i-PrOH, THF, 0 °C
93% yield
37.2:37.3, 1:1.3
MeO$_2$C
OH
Me
37.2
+
MeO$_2$C
OH
Me
37.3

Scheme 37

In work on the formal synthesis of (±)-homogynolide-B [a substance isolated from *Homogyne alpina. (L.) Cass*], Srikrishna and his colleagues[40] used 5-*exo*-digonal radical cyclization (Scheme 38) to produce the spirolactone unit. Bromoacetals **38.2** underwent highly stereoselective radical cyclization to produce spiroacetals **38.3**, which were easily

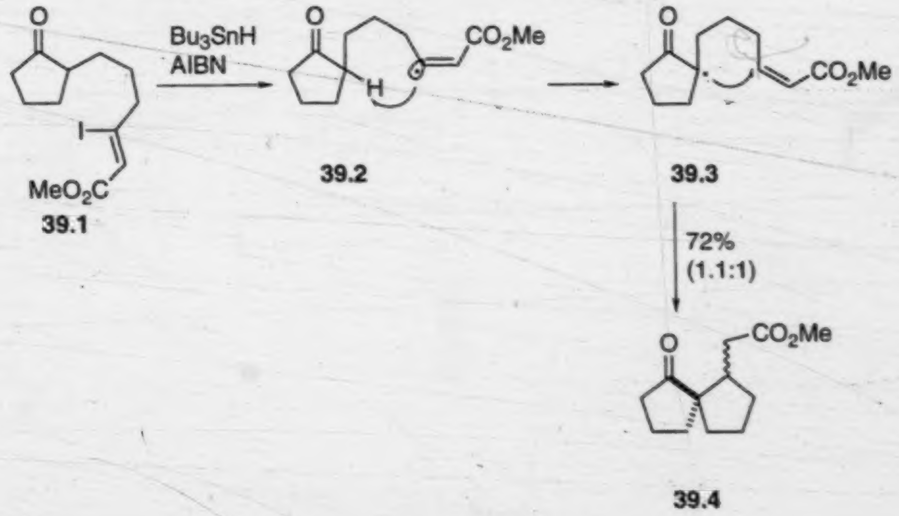

O
O
OMe
H
38.1
OH
NBS
89%
MeO
O
Br
38.2
Bu$_3$SnCl
NaCNBH$_3$
AIBN
t-BuOH
76%
OMe
O
38.3
2 M HCl
80%
OH
38.4
PCC
silica gel
93%
O
38.5
38.6

Scheme 38

converted into spirolactone **38.5**. This had previously been converted into (±)-homogynolide-B (**38.6**).[40c] It is not clear what controls the regioselectivity of the radical cyclization.

c. *Hydrogen transfer and radical cyclization*

A 1,5-hydrogen atom transfer from the α-position of a cycloalkanone, followed by radical cyclization, has been used by Sha and his colleagues[41] to generate spirocenters in a stereocontrolled manner (Scheme 39). Under standard radical conditions, cyclic ketones bearing a β-iodo-α,β-unsaturated ester appendage, such as **39.1**, first underwent a 1,5 hydrogen transfer to give **39.3**, and then underwent a 5-*exo*-trigonal radical cyclization to afford spirocycles **39.4**.



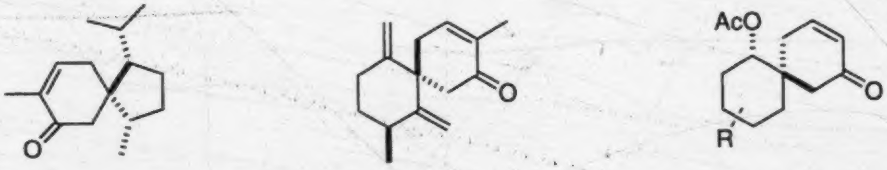
Scheme 39

1.7 Conclusion

The above summary confirms the impression gained from earlier reviews that the stereocontrolled formation of spirocompounds is rarely a simple task, but that elagant solutions can be found.

2 RESULTS AND DISCUSSION

Asymmetric centers occur frequently in natural products, and a number of sesquiterpenes, such as acorenone B[42] (**1**) and (6*S*,10*S*)-3,10-dimethyl-7,11-dimethylidenespiro[5,5]undec-2-en-4-one (**2**),[43] contain spirocenters with enone functional groups. This encouraged us to develop a method for making spiroenones of type **3**, in such a way that the stereochemistry at the spirocenter is controlled by the stereochemistry of an adjacent hydroxyl group.[1,44]



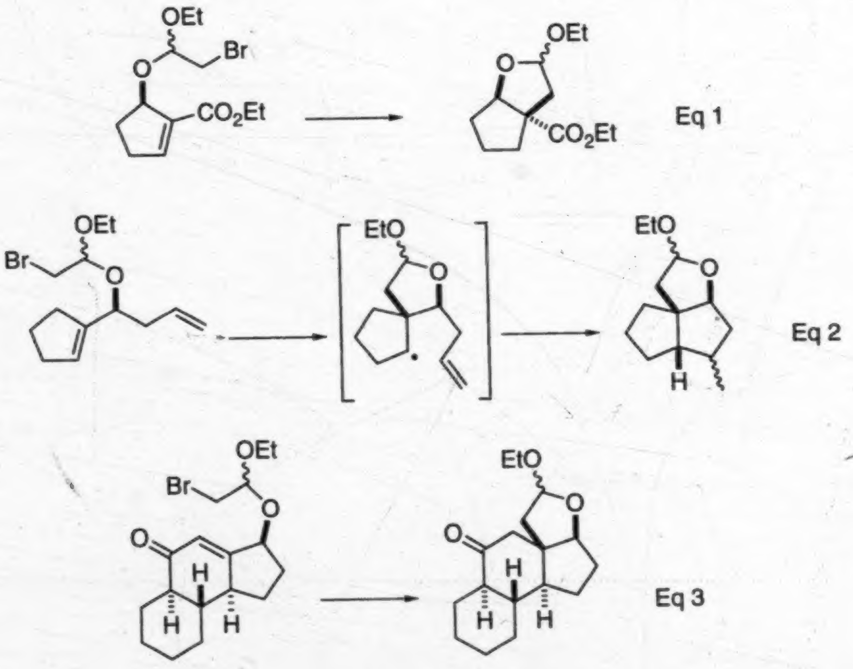
1
acorenone B

2

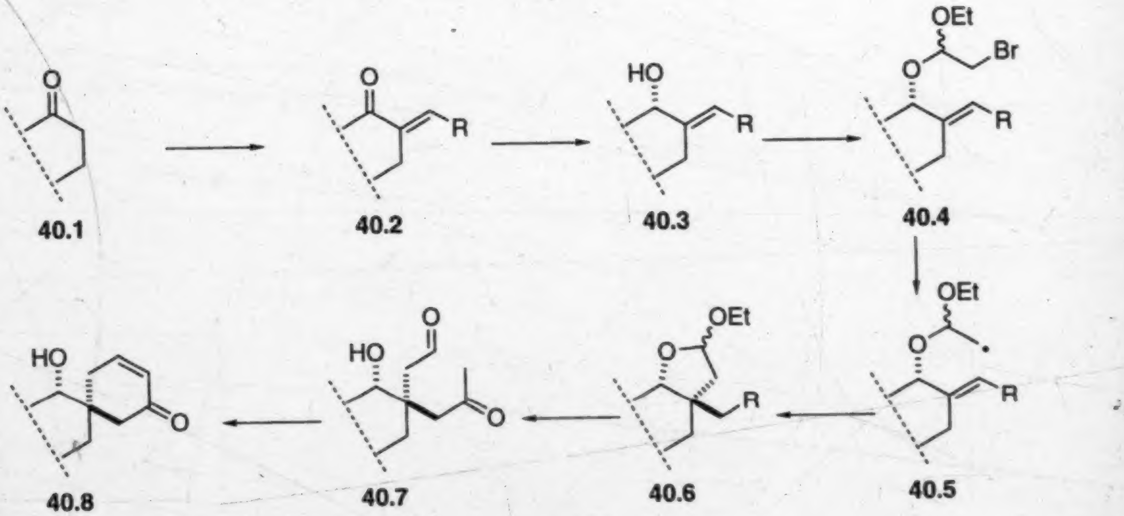
3

Figure 1 Structures of **1**, **2** and **3**

Radical cyclizations of haloacetals onto fully substituted sp^2 centers are known, as illustrated by the examples of equations 1,[45] 2,[46] and 3,[47] but the process[48] does not appear to have been exploited specifically as a general and stereochemically controllable method for the preparation of spirocompounds. Our plan was to develop the cyclization of bromoacetals for making spirocompounds with stereochemical control, as summarized in Scheme 40. We felt that radical closure onto an exocyclic double bond, as in **40.5** → **40.6**, rather than onto one that is endocyclic, would be more convenient, because in the former case the requisite alkenes should be available easily by aldol reaction and dehydration.[49]


OEt
Br
O
CO2Et
OEt
O
CO2Et
Eq 1
OEt
Br
O
EtO
O
EtO
O
H
Eq 2
OEt
Br
O
O
H
H
H
EtO
O
O
H
H
H
Eq 3

Equations 1,2,3

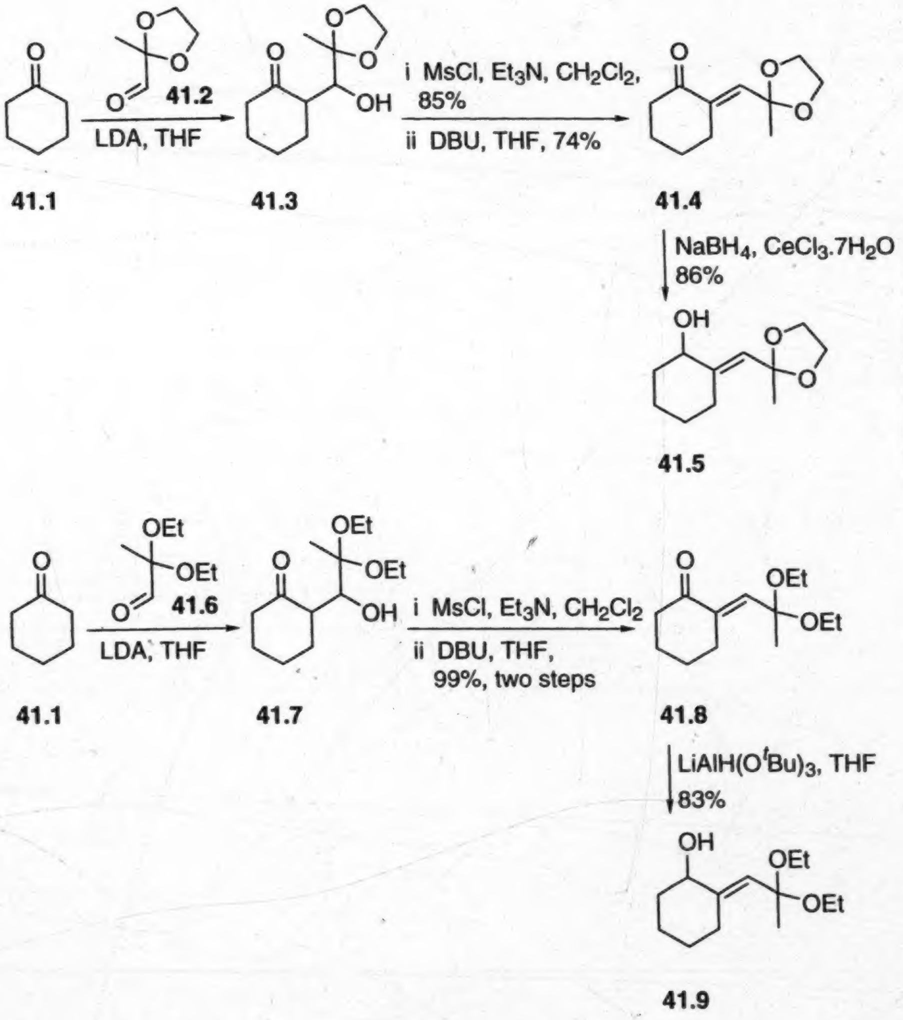

O
40.1
O
R
40.2
HO
R
40.3
OEt
Br
O
R
40.4
OEt
O
R
40.5
OEt
O
R
40.6
HO
O
O
40.7
HO
O
40.8

Scheme 40

In the approach shown in Scheme 40, R is a group that is convertible into a methyl ketone unit [MeC(O)]. The radical cyclization sets up the spirocenter (**40.4** → **40.5** → **40.6**) with the stereochemistry as shown, because 5-*exo*-trigonal cyclizations that generate a five-membered ring on an existing five- or six-membered ring give *cis* ring fused products.[50] A subsequent intramolecular aldol condensation would then form the enone functional system (**40.7** → **40.8**).

2.1 Exploratory studies

On the basis of the above outline, our initial approach (Scheme 41) called for conversion of cyclohexanone into the conjugated ketone **41.4**, which was prepared by aldol condensation with aldehyde **41.2**,[51] followed by mesylation and treatment with DBU (**41.1** → **41.3** → **41.4**). Compound **41.4** was not fully characterized, as this route was ultimately unsuccessful, and the double bond geometry shown is an arbitrary assignment, but is probably correct, on the basis of arguments given below for the related compound **42.3**. Sodium borohydride reduction of enone **41.4** in the presence of $CeCl_3 \cdot 7H_2O$ produced alcohol **41.5** in 86% yield, but the alcohol was unstable, and it was not possible to attach the bromoacetal unit efficiently by treatment with ethyl vinyl ether and NBS in CH_2Cl_2. Likewise, bromoacetal formation was not possible in the corresponding diethyl ketal series, starting with diethyl ketal **41.6**[52] (**41.1** → **41.7** → **41.8** → **41.9**).

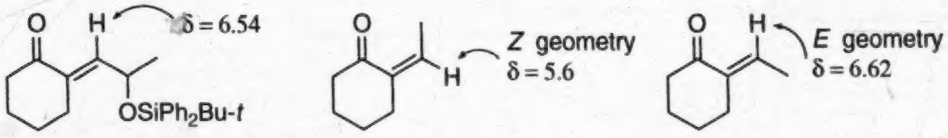

41.2
LDA, THF
i MsCl, Et3N, CH2Cl2, 85%
ii DBU, THF, 74%
41.1
41.3
41.4
NaBH4, CeCl3.7H2O
86%
41.5
41.6
LDA, THF
i MsCl, Et3N, CH2Cl2
ii DBU, THF, 99%, two steps
41.1
41.7
41.8
LiAlH(OtBu)3, THF
83%
41.9

Scheme 41

2.2 Synthesis of a spiroenone containing two six-membered rings

Because of our inability to make bromoacetals from **41.5** or **41.9**, we modified the approach to that summarized in Scheme 42 and Scheme 43, and found that this revised approach worked quite easily.

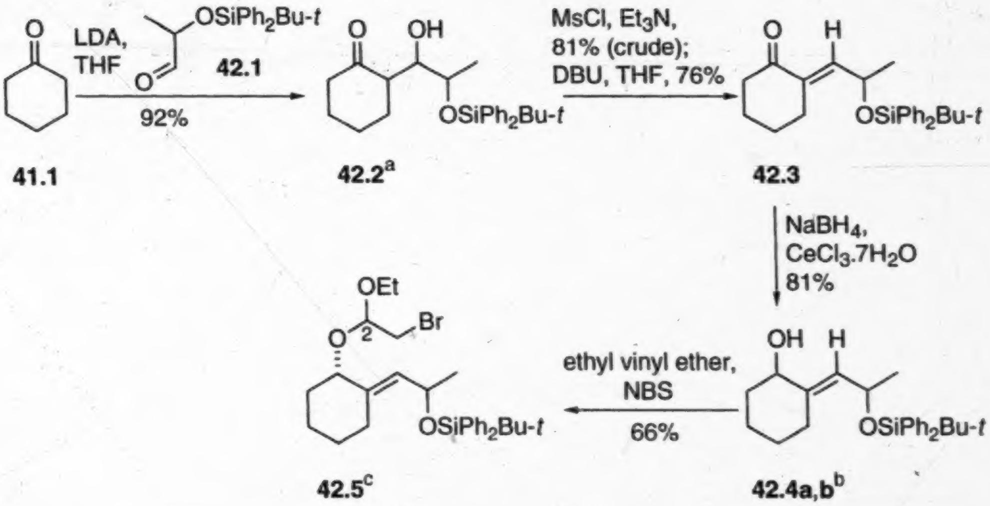
Aldol condensation of cyclohexanone with the readily available aldehyde **42.1**[53] gave the expected aldols **42.2**,[54] and these could be dehydrated easily by mesylation and then treatment with DBU. Enone **42.3** was obtained with the *E* geometry, as shown. This assignment is based on a comparison with literature chemical shift data for compounds **4** and **5**.[55] The olefinic proton chemical shift (δ) of enone **42.3** is 6.54 ppm, a value which matches very well with that for the *E* isomer **5** (δ = 6.62 ppm) rather than with that reported for compound **4** (δ = 5.6 ppm) having the *Z* geometry (Figure 2).



42.3 **4** **5**

Figure 2 The olefinic proton chemical shift (δ) of **42.3**, **4** and **5**

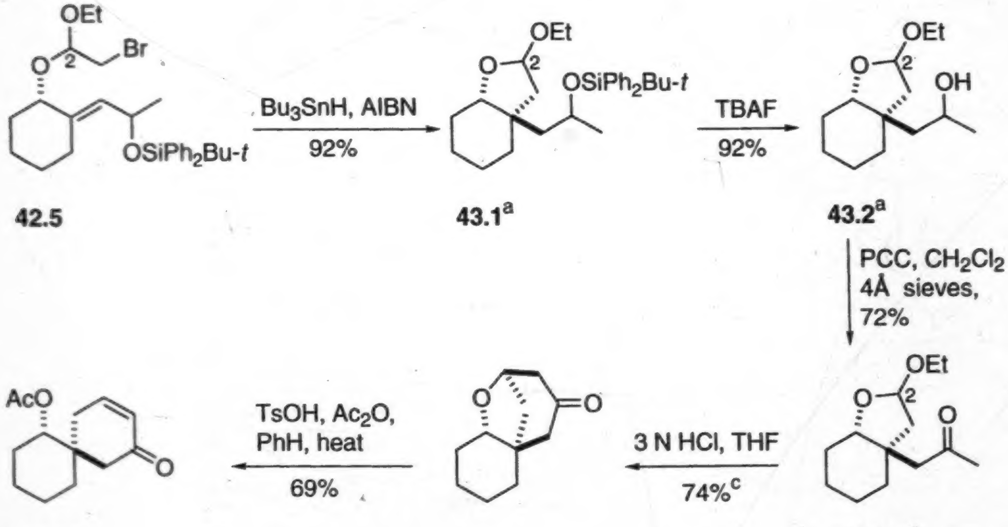
Reduction of enone **42.3** with $NaBH_4$-$CeCl_3.7H_2O$ afforded the expected alcohols **42.4**. These could be separated; the yield of the major alcohol was 65%, while that of the minor diastereoisomer was 16%. As the latter was a very minor component of the mixture, only the major alcohol was taken further. Treatment with ethyl vinyl ether in the presence of NBS served to generate the required bromoacetals **42.5** (66%) (Scheme 42), which we could now use to test our plan for making spirocompounds.


LDA, THF
OSiPh$_2$Bu-*t*
42.1
92%
41.1
42.2^a
MsCl, Et$_3$N, 81% (crude); DBU, THF, 76%
42.3
NaBH$_4$, CeCl$_3$.7H$_2$O 81%
ethyl vinyl ether, NBS
66%
42.4a,b^b
42.5^c
OEt
Br
2

Scheme 42

Legend for Scheme 42. (a) One main diastereoisomer. (b) major diastereoisomer (**42.4a**) isolated in 65% yield, minor diastereoisomer (**42.4b**) isolated in 16% yield. Only major diastereoisomer taken further. (c) Mixture (ca 1:1) of two diastereoisomers differing in stereochemistry at C(2). Relative stereochemistry of ring and side chain stereogenic centers not assigned.

The radical cyclization (**42.5** → **43.1**) worked nicely on rapid heating (115 °C) with a mixture of Bu_3SnH (ca 2 equiv) and AIBN in PhMe. Under these optimized conditions[56] the desired cyclization products **43.1** were isolated in high yield (92%) as two inseparable diastereoisomers (ca 4:3) differing in stereochemistry at C(2). The *cis* ring fusion is assigned as shown, based on the rules for ring fusion stereochemistry.[50] The (phenylseleno)acetal corresponding to **42.5** (PhSe instead of Br), which was available in comparable yield to the bromoacetal (ethyl vinyl ether, PhSeBr, 70%) underwent radical cyclization in much poorer yield (60%), and so only bromoacetals were used in subsequent work. Desilylation of **43.1** by using Bu_4NF gave alcohol **43.2** in 92% yield, and PCC oxidation in the presence of 4 Å molecular sieves converted the angular substituent into a methyl ketone (**43.2** → **43.3**), which was obtained as two separate diastereoisomers: the major diastereoisomer (**43.3a**) was isolated in 41% yield, and the minor diastereoisomer (**43.3b**) in 31% yield. Exposure of a mixture of **43.3a** and **43.3b** to mineral acid (3 N hydrochloric acid) in THF caused hydrolysis of the lactol


OEt
O
2
Br
OSiPh2Bu-t
42.5
Bu3SnH, AIBN
92%
OEt
O
2
OSiPh2Bu-t
43.1a
TBAF
92%
OEt
O
2
OH
43.2a
PCC, CH2Cl2
4Å sieves,
72%
OEt
O
2
O
43.3a,bb
3 N HCl, THF
74%c
O
O
43.4
TsOH, Ac2O,
PhH, heat
69%
AcO
O
43.5

Scheme 43

Legend for Scheme 43. (a) Two inseparable diastereoisomers (ca 4:3) differing in stereochemistry at C(2). (b) Major diastereoisomer (**43.3a**) isolated in 41% yield, minor diastereoisomer (**43.3b**) in 31% yield. Compounds **43.3a** and **43.3b** differ in stereochemistry at C(2). (c) Mixture of **43.3a** and **43.3b** used.

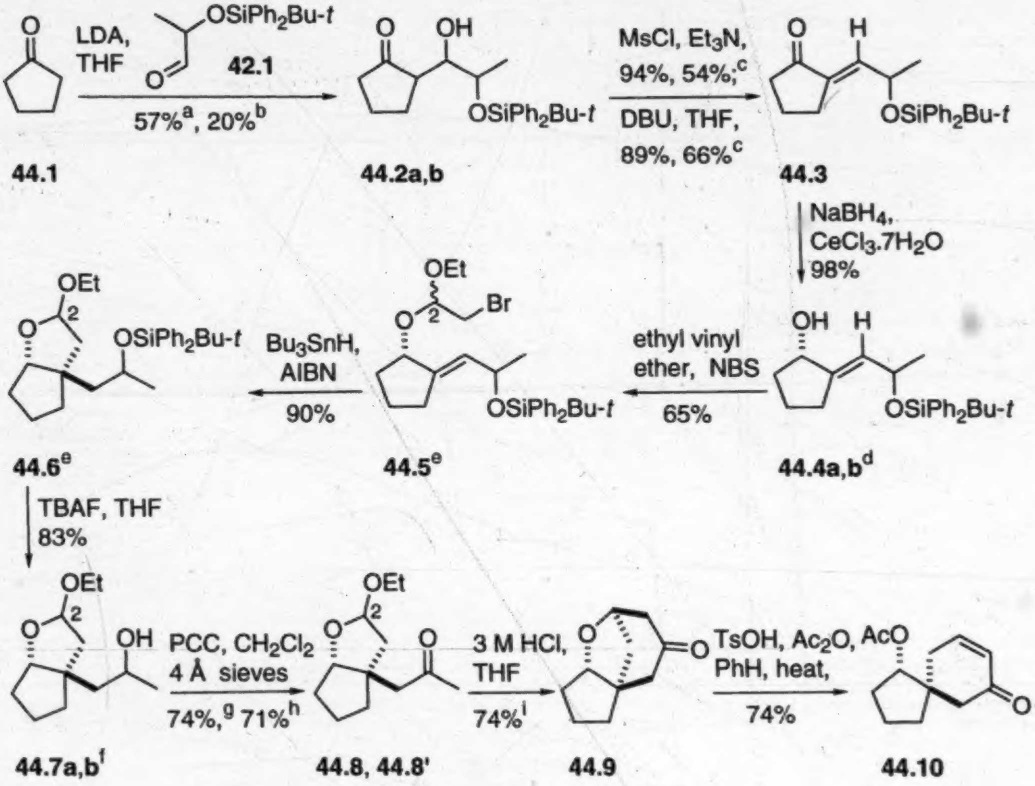
ethyl ethers to the corresponding lactols, and induced dehydration and intramolecular aldol condensation (cf. Scheme 40, **40.6** → **40.7** → **40.8**), leading to **43.4**. Finally, the enone system of the targeted spiroenone compound **43.5** was liberated[57] by heating **43.4** in PhH with Ac_2O and a catalytic amount of $TsOH.H_2O$.

Although use of **42.1**, as opposed to **41.2**, means that more complex stereoisomer mixtures have to be handled, the silyl ether series based on **42.1** has the important advantage that it does not involve any especially sensitive intermediates.

2.3 Synthesis of a spiroenone containing a six- and a five-membered ring

With this successful method of making spiroenone (**43.5**) starting from cyclohexanone in hand, we then repeated the sequence, starting from cyclopentanone; the results were entirely comparable, and are summarized in Scheme 44.

Aldol condensation of cyclopentanone (**44.1**) with aldehyde **42.1** afforded aldol **44.2** as two separable diastereoisomers in 57% (**44.2a**) and 20% (**44.2b**) yield, respectively. Dehydration of both **44.2a** and **44.2b** gave the same enone **44.3** in moderated yield. The *E* geometry was again assigned by comparison of the chemical shift of the olefinic hydrogen of **44.3** ($\delta = 6.50$ ppm) with literature values.[55] Sodium borohydride reduction in the presence of $CeCl_3 \cdot 7H_2O$ gave the allylic alcohol **44.4** as two separable diastereo-


LDA,
THF
OSiPh$_2$Bu-t
42.1
57%^{a}, 20%^{b}
44.1
44.2a,b
MsCl, Et$_3$N,
94%, 54%;^{c}
DBU, THF,
89%, 66%^{c}
44.3
NaBH$_4$,
CeCl$_3$.7H$_2$O
98%
ethyl vinyl
ether, NBS
65%
44.4a,b^d
Bu$_3$SnH,
AIBN
90%
44.5^e
44.6^e
TBAF, THF
83%
PCC, CH$_2$Cl$_2$
4 Å sieves
74%,^{g} 71%^{h}
44.7a,b^f
44.8, 44.8'
3 M HCl,
THF
74%^{i}
44.9
TsOH, Ac$_2$O,
PhH, heat,
74%
44.10

Scheme 44

Legend for Scheme 44. (a) Yield of major aldol (**44.2a**), which contains trace impurities. (b) Yield of minor aldol (**44.2b**), which contains trace impurities. (c) First yield in each case corresponds to major aldol series. (d) Major diastereoisomer (**44.4a**) isolated in 55% yield, minor diastereoisomer (**44.4b**) in 43% yield. Only major diastereoisomer was taken further. (e) Mixture (1:1) of two inseparable diastereoisomers differing in stereochemistry at C(2). (f) Major diastereoisomer (**44.7a**) isolated in 44% yield, minor diastereoisomer (**44.7b**) in 39% yield. The diastereoisomers differ in stereochemistry at C(2). (g) Yield of **44.8** from **44.7a** (major diastereoisomer of **44.7**). (h) Yield of **44.8′** from **44.7b** (minor diastereoisomer of **44.7**). Compounds **44.8** and **44.8′** differ in stereochemistry at C(2). (i) Mixture of **44.8** and **44.8′** used.

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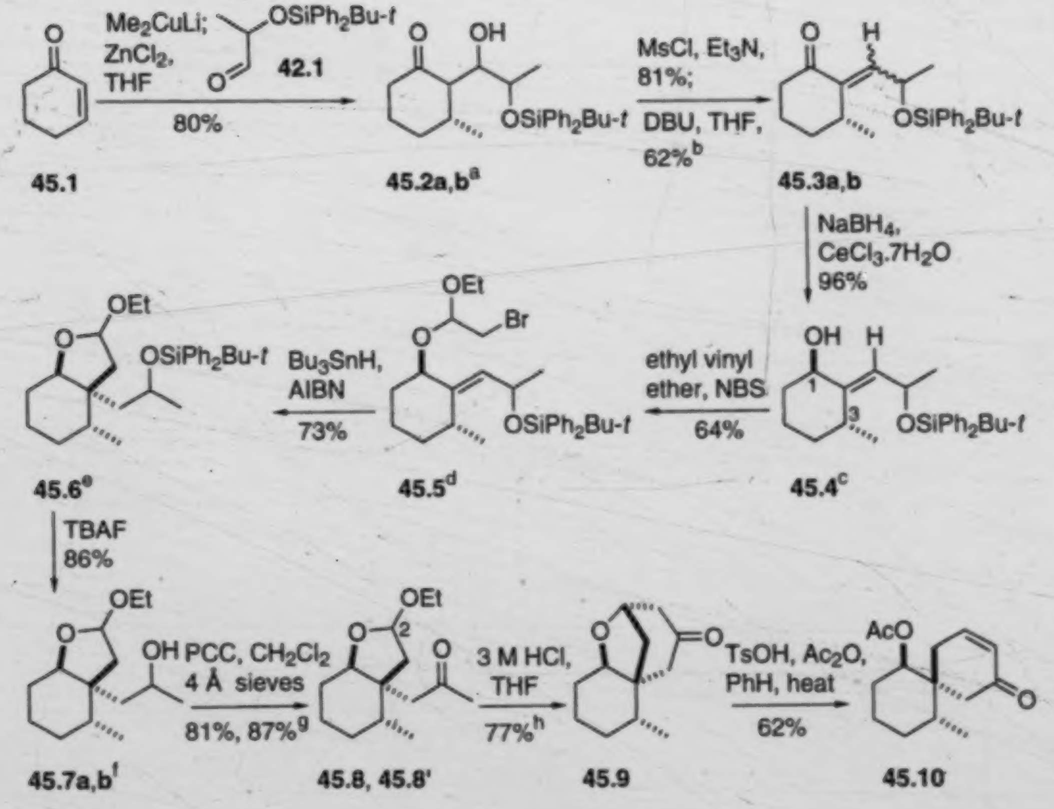
isomers: 55% for the major diastereoisomer (**44.4a**) and 43% for the minor diastereoisomer (**44.4b**). Only the major diastereoisomer (**44.4a**) was treated with ethyl vinyl ether and NBS to produce bromoacetals **44.5** as a 1:1 inseparable mixture of diastereoisomers. The key radical cyclization was again successful and the desired cyclization products **44.6** were isolated in 90% yield. Desilylation of **44.6** (Bu_4NF) and PCC oxidation gave the separable methyl ketones **44.8** and **44.8′** in good yields. The spiroenone **44.10** could be produced by treating a mixture of **44.8** and **44.8′** with hydrochloric acid, followed by Ac_2O and *p*-$TsOH.H_2O$ (74% for each step).

2.4 The synthesis of spiroenones with a methyl group as a stereochemical marker

The experiments leading to **43.5** and **44.10** suggested that the method may be general, and so we next established that the stereochemistry of the spirocenter could indeed be reversed by appropriate manipulation of the stereochemistry of the adjacent oxygen function. In order to do this, the route of Schemes 42 and 43 was modified by incorporating a methyl group as a stereochemical marker in the 6-membered ring (see Scheme 45). A conjugate addition and aldol condensation were used to convert 2-cyclohexenone into **45.2a,b** in 80% overall yield (Scheme 45), and then our standard sequence of reactions was applied, as shown in Scheme 45. The presence of the methyl group increased the number of isomers in the intermediate stages, but this complication disappears, of course, near the end of the sequence. Both diastereoisomers of aldol **45.2** were dehydrated to give **45.3** as two separable fractions (each fraction consists two diastereoisomers). The major fraction of enone **45.3** (53% yield, consisting of two diastereoisomers, each with *E*-geometry) was used for the subsequent steps. The *E* geometry for **45.3a** was established by the characteristic chemical shift of the vinylic hydrogen (δ 6.4 ppm).[55] Both diastereoisomers of the minor fraction of **45.3** had *Z* geometry (δ 5.6 ppm).[55] Compound **45.4** was obtained as an 8:1 mixture of *E* diastereoisomers from **45.3a** (96%). The relative stereochemistry at C(1) and C(3) of each component was inferred by observation of an NOE (ca 5%) between C(1)**H** and the C(3)C**H**$_3$ hydrogens. The origin of the *trans* relationship of the hydroxyl and methyl groups in **45.4** remains unclear to us since the usual (at least for cyclohexenones with endo double bonds[58]) axial hydride delivery in $NaBH_4$ reduction would give the opposite stereochemistry. Bromoacetal formation (64% of a mixture of four diastereoisomers 8:8:1:1), followed by radical cyclization (73%), gave **45.6** as a mixture of four diastereoisomers. In this case (**45.6**), however, the diastereoisomer ratio could not be determined from the ^{1}H NMR spectrum, but the presence of two major and two minor diastereoisomers was clear from the ^{13}C NMR spectrum. Desilylation (Bu_4NF) afforded alcohols **45.7** as a separable mixture of two fractions in yields of 44% and 42%,

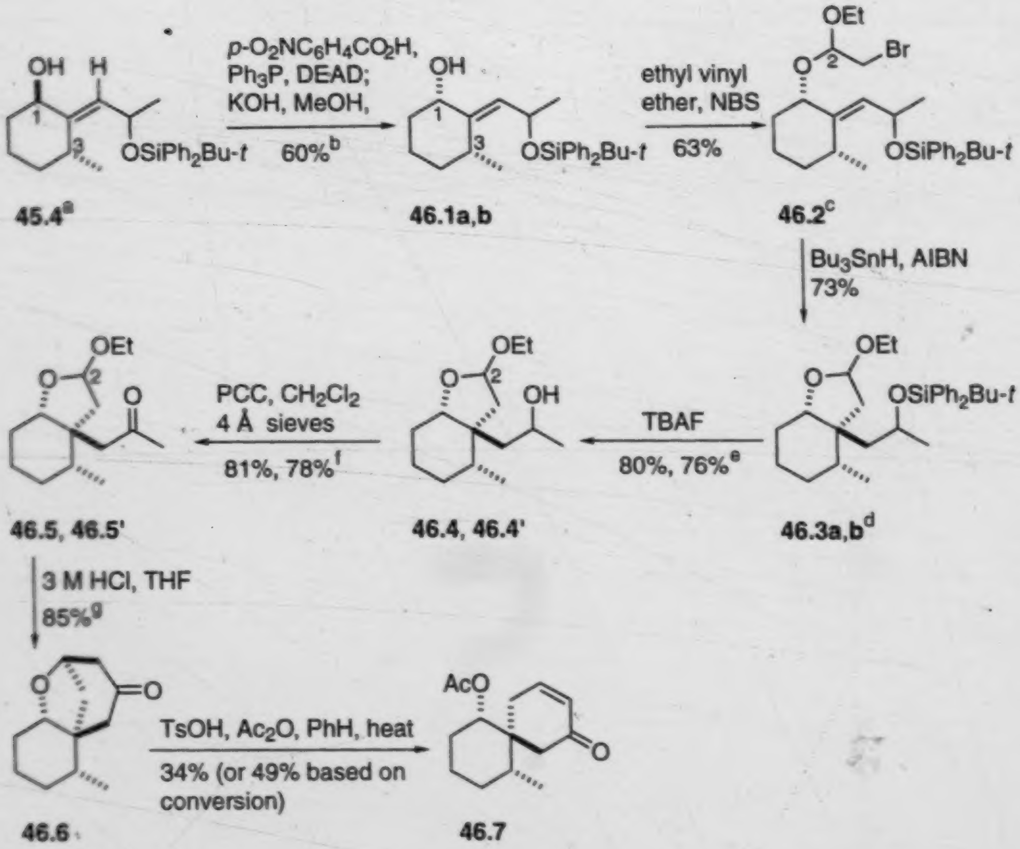

45.1
Me2CuLi; ZnCl2, THF
42.1
OSiPh2Bu-t
80%
45.2a,b^a
MsCl, Et3N, 81%; DBU, THF, 62%^b
45.3a,b
NaBH4, CeCl3.7H2O 96%
45.4^c
ethyl vinyl ether, NBS 64%
45.5^d
Bu3SnH, AIBN 73%
45.6^e
TBAF 86%
45.7a,b^f
PCC, CH2Cl2 4 Å sieves 81%, 87%^g
45.8, 45.8'
3 M HCl, THF 77%^h
45.9
TsOH, Ac2O, PhH, heat 62%
45.10
OEt
Br
AcO
1
2
3

Scheme 45

Legend for Scheme 45. (a) Major diastereoisomer (**45.2a**) 72% yield, minor diastereoisomer (**45.2b**) 8% yield. (b) Mixture of diastereoisomers of **45.2** used. Yield of major fraction (**45.3a**, two diastereoisomers (ca 8:1), both with *E* geometry) 53%, yield of minor fraction (**45.3b**, two diastereoisomers (ca 5:1), both *Z* geometry) 9%. Only major fraction (**45.3a**) taken forward. (c) Two inseparable diastereoisomers (ca 8:1). (d) Four diastereoisomers (ca 8:8:1:1). (e) Four diastereoisomers. (f) Major fraction (**45.7a**) 44%, minor fraction (**45.7b**) 42%, each fraction consisting of two diastereoisomers (both ca 6:1). (g) Yield from **45.7a** (major fraction of **45.7**) 81%; yield from **45.7b** (minor fraction of **45.7**) 87%. Both **45.8** and **45.8′** were single diastereoisomers differing in stereochemistry at C(2). (h) A 1:1 mixture of **45.8** and **45.8′** was used.

each consisting of two diastereoisomers, and in both cases, the isomer ratio was ca 6:1 (by ^{1}H NMR measurement). After oxidation with PCC, each fraction gave a single diastereoisomer of general structure **45.8/45.8′** in over 80% yield. Both of ketones **45.8** and **45.8′**, which differ only in the stereochemistry at C(2), were then treated with hydrochloric acid to afford the same tricyclic product **45.9** (77%). This was converted as before, by exposure to Ac_2O and TsOH in refluxing PhH, into spiroenone **45.10** (62%).

Compound **45.4** can also serve as an intermediate for generating the other stereochemistry at the spirocarbon, and this was demonstrated as follows. Alcohols **45.4** (as an 8:1 diastereoisomer mixture at the carbon bearing the siloxy group) were subjected to Mitsunobu inversion (Scheme 46, **45.4** → **46.1a,b**) and allylic alcohol **46.1** was isolated as two diastereoisomers (48% yield for the major diastereoisomer **46.1a** and 12% for the minor diastereoisomer **46.1b**). The relative stereochemistry at C(1) and C(3) in alcohol **46.1a** was also examined by NOE measurements. Unlike the case with **45.4**, there was no NOE enhancement between C(1)**H** and the C(3)C**H**$_3$ hydrogens, and this is consistent with the *cis* relationship of the C(3) methyl and C(1) hydroxyl groups in **46.1a**. The major alcohol (**46.1a**) was converted into bromoacetals **46.2** in 63% yield as a 1:1 mixture of diastereoisomers. These were subjected (as a mixture) to radical cyclization and the individual products (**46.3a**, 49% and **46.3b**, 24%) were separately desilylated (80% for **46.3a**,



45.4[a]
p-O2NC6H4CO2H, Ph3P, DEAD; KOH, MeOH, 60%[b]
46.1a,b
ethyl vinyl ether, NBS 63%
46.2[c]
Bu3SnH, AIBN 73%
46.3a,b[d]
TBAF 80%, 76%[e]
46.4, 46.4'
PCC, CH2Cl2 4 Å sieves 81%, 78%[f]
46.5, 46.5'
3 M HCl, THF 85%[g]
46.6
TsOH, Ac2O, PhH, heat 34% (or 49% based on conversion)
46.7

Scheme 46

Legend for Scheme 46. (a) An 8:1 mixture of diastereoisomers. (b) Yield of major diastereoisomer (**37a**) 48% overall. Yield of minor diastereoisomer (**37b**) 12%. Only major diastereoisomer taken further. (c) Two diastereoisomers (ca 1:1) differing in stereochemistry at C(2). (d) Yield of major diastereoisomer (**39a**) 49%, yield of minor diastereoisomer (**39b**) 24%. (e) Yield of **40** from **39a** (major diastereoisomer of **39**) 80%, yield of **40′** from **39b** (minor diastereoisomer of **39**) 76%. Isomers **40** and **40′** differ in stereochemistry at C(2). (f) Yield of **41** from **40** (major diastereoisomer series) 81%, yield of **41′** from **40′** (minor diastereoisomer series) 78%. (g) Ketones **41** and **41′** were mixed (ca 2:1) before treatment with HCl.

and 76% for **46.3b**). Oxidation of the alcohols (**46.4** → **46.5** and **46.4′** → **46.5′**) gave the expected ketones in ca 80% yield. Samples of these were mixed and converted into the tricyclic ketone **46.6** in 85% yield by treatment with hydrochloric acid. Finally, heating with Ac_2O in the presence of $TsOH.H_2O$ yielded spiroenone **46.7**. The compound was, of course, isomeric with **45.10**, obtained from alcohols **45.4**.

3. CONCLUSION

The above experiments show that the present methodology can be used to make spiroenones in such a way that the stereochemistry of the spirocenter can be controlled, and either stereochemistry can be generated. The spiroenones could be generated with two six-membered rings (**43.5**) starting from simple cyclohexanones. Alternatively, a six-membered ring spirofused to a five-membered ring (**44.10**) can be generated, starting from cyclopentanones. The stereochemistry of the spirocenter can be inverted (**45.10** and **46.7**) simply by including a Mitsunobu inversion at the stage of the precursor alcohol (see **45.4**). Although our method does provide the intended control of stereochemistry, this is achieved at the cost of a rather long sequence, and we decided not to evaluate the method in natural product synthesis.

4 EXPERIMENTAL

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[59] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexanes used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Cannula transfers were done under slight pressure (N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid[60] or *p*-anisaldehyde,[61] followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O

were distilled from sodium and benzophenone ketyl.

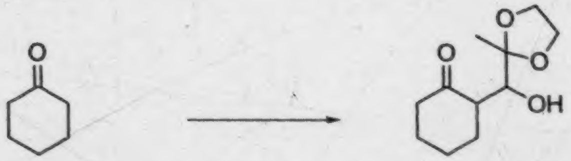
FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

^{1}H nuclear magnetic resonance spectra were recorded with Bruker AM spectrometers (at 300, 360 and 400 MHz), or Varian INOVA spectrometers (at 300, 400 and 500 MHz) in the specified deuterated solvent at 27.5 °C. ^{13}C spectra were recorded with Bruker AM spectrometers (at 75.5 and 100.6 MHz) or Varian UNITY or INOVA spectrometers (at 100.6 and 125.7 MHz) at 27.5 °C. The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment. In cases where the number of signals is less than expected, we assume this is due to coincident chemical shifts.

Mass spectra were recorded with AEI Models MS-12, MS-50 MS-9 (modified), Kratos MS-50 (modified) or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

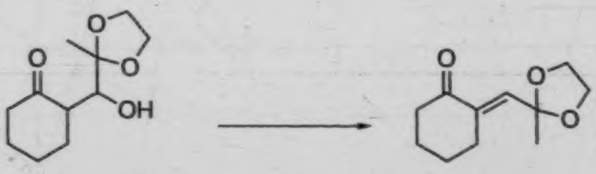
2-[Hydroxy[2-methyl[1,3]dioxolan-2-yl)methyl]]-cyclohexanone (41.3).



41.1 **41.3**

Cyclohexanone (0.23 mL, 2.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [generated by dropwise addition of BuLi (2.5 M, 0.89 mL, 2.2 mmol) to *i*-Pr$_2$NH (0.32 mL, 2.3 mmol) in THF (15 mL) at 0 °C, followed, after 15 min, by cooling to -78 °C]. After 1 h, aldehyde **41.2**[51] (0.1286 g, 1.107 mmol) in THF (5 mL) was injected quickly. Stirring was continued for 30 min at -78 °C. The cooling bath was removed, stirring was continued for 1 h, and the reaction was quenched with saturated aqueous NH$_4$Cl (6 mL). The mixture was diluted with Et$_2$O (150 mL), washed with brine, dried (MgSO$_4$), and evaporated. Flash chromatography of the residue over silica gel (1.1 x 20 cm), using 1:1 EtOAc-hexane, gave alcohols **41.3** (52 mg, 22%) as a colorless oil, which was used directly without characterization.

(*E*)-2-(2-Methyl[1,3]dioxolan-2-ylmethylene)cyclohexanone (41.4).

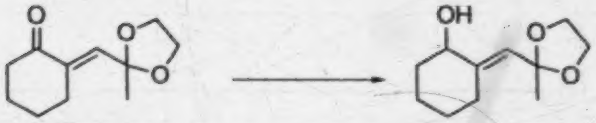


41.3 **41.4**

$MeSO_2Cl$ (56.7 μL, 0.728 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **41.3** (52.0 mg, 0.243 mmol) and Et_3N (0.17 mL, 1.2 mmol) in CH_2Cl_2 (5 mL). The cooling bath was left in place, but was not recharged, and stirring was continued for 18 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (1.5 mL), diluted with Et_2O (20 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (10 mL) as a rinse. Evaporation of the filtrate gave the crude mesylates (60.0 mg, 85%), which were used immediately for next step.

DBU (0.064 mL, 0.42 mmol) was added dropwise to a stirred solution of the above mesylates (60.0 g, 0.205 mmol) in THF (3 mL). After 7 h, the mixture was diluted with Et_2O (20 mL) and washed with water, saturated aqueous NH_4Cl, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.1 x 20 cm), using 1:4 EtOAc-hexane, gave enone **41.4** (29.9 mg, 74%) as an oil: ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.47 (s, 3 H), 1.63-1.91 (m, 4 H), 2.41 (t, J = 6.8 Hz, 2 H), 2.75 (dt, J = 2.0, 6.2 Hz, 2 H), 3.76-3.97 (m, 4 H), 6.30 (t, J = 2.0 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 24.0 (t), 24.2 (t), 24.7 (q), 27.5 (t), 41.1 (t), 64.7 (t), 108.1 (s), 137.2 (d), 139.7 (s), 201.6 (s).

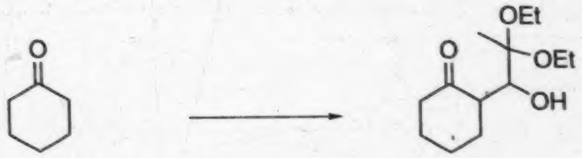
(*E*)-2-(2-Methyl[1,3]dioxolan-2-ylmethylene)cyclohexanol (41.5).



41.4 **41.5**

$NaBH_4$ (2.3 mg, 0.062 mmol) was added to a stirred and cooled (0 °C) solution of enone **41.4** (8.0 mg, 0.041 mmol) and $CeCl_3.7H_2O$ (22.8 mg, 0.0612 mmol) in MeOH (1 mL). After 5 min, the cooling bath was removed and stirring was continued for 30 min. The mixture was quenched with saturated aqueous NH_4Cl (5 drops), diluted with Et_2O (5 mL), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (10 mL) as a rinse. The filtrate was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 15 cm), using 1:2 EtOAc-hexane, gave alcohol **41.5** (7.5 mg, 93%) as a single isomer (^{13}C NMR): ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.21-2.08 (m, 11 H), 2.81-2.93 (m, 1 H), 3.77-4.02 (m, 5 H), 5.44 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 24.0 (t), 26.1 (q), 27.1 (t), 27.9 (t), 37.5 (t), 64.4 (t), 64.5 (t), 73.5 (d), 108.5 (s), 122.5 (d), 146.2 (s).

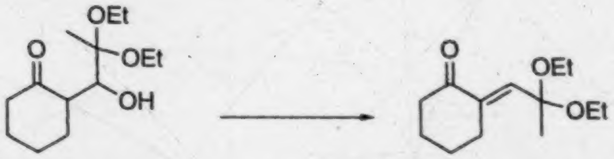
2-(2,2-Diethoxy-1-hydroxypropyl)cyclohexanone (41.7).



41.1 **41.7**

Cyclohexanone (0.18 mL, 1.7 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [generated by dropwise addition of BuLi (2.5 M, 3.9 mL, 9.7 mmol) to *i*-Pr_2NH (1.4 mL, 10.0 mmol) in THF (60 mL) at 0 °C, followed, after 15 min, by cooling to -78 °C]. After 1 h, aldehyde **41.6**[52] (0.1730 g, 1.183 mmol) in THF (5 mL) was injected quickly. Stirring was continued for 5 min at -78 °C. The cooling bath was removed and stirring was continued for 40 min. The mixture was cooled to 0 °C and was quenched with saturated aqueous NH_4Cl (3 mL). The cooling bath was removed and stirring was continued until the mixture had reached room temperature (ca 45 min). The mixture was diluted with Et_2O (100 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over alumina (Grade III) (1.1 x 15 cm), using 1:4 EtOAc-hexane, gave alcohols **41.7** (0.183 g, 63%) as a single diastereoisomer (^{13}C NMR): FTIR (CH_2Cl_2, cast) 3371, 2974, 2932, 2894, 2865, 1694 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.90-1.84 (m, 14 H), 2.01-2.66 (m, 5 H), 3.18-3.37 (m, 4 H), 4.33-4.50 (m, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 14.9 (q), 15.3 (q), 17.0 (q), 22.2 (t), 27.9 (t), 28.7 (t), 41.5 (t), 52.7 (d), 55.2 (t), 56.3 (t), 68.8 (d), 102.6 (s).

(*E*)-2-(2,2-Diethoxypropylidene)cyclohexanone (41.8).



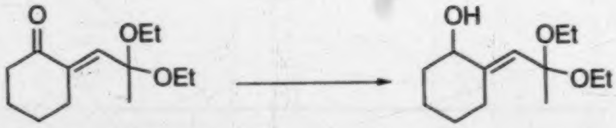
41.7 **41.8**

$MeSO_2Cl$ (0.175 mL, 2.24 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **41.7** (0.1826 g, 0.7473 mmol) and Et_3N (0.52 mL, 3.7 mmol) in PhH (10 mL). After 2 h at 0 °C, the cooling bath was removed and stirring was continued for 10 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (4 mL), diluted with Et_2O (50 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (2 x 2 cm) of alumina (grade III), using Et_2O (20 mL) as a rinse. Evaporation of the filtrate gave the crude mesylates (245 mg, ca 100%), which were used immediately for next step.

DBU (0.23 mL, 1.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the above mesylates (245 mg, ca 0.7473 mmol) in THF (8 mL). The cooling bath was removed and stirring was continued for 8 h. The mixture was diluted with Et_2O (50 mL) and washed with water, saturated aqueous NH_4Cl, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over alumina (grade III) (1.1 x 20 cm), using 1:6 EtOAc-hexane, gave enone **41.8** (0.167 g,

99%) as an oil: FTIR (CH_2Cl_2 cast) 2975, 2933, 2883, 2730, 1694, 1629 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.14 (t, J = 7.1 Hz, 6 H), 1.31-1.46 (m, 7 H), 2.21-2.29 (m, 2 H), 2.59-2.68 (m, 2 H), 3.41 (q, J = 7.1 Hz, 4 H), 6.87 (t, J = 2.0 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.3 (q), 23.2 (q), 23.5 (t), 23.6 (t), 27.2 (t), 40.5 (t), 56.3 (t), 100.7 (s), 137.9 (d), 139.2 (s), 199.1 (s); exact mass *m/z* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1562.

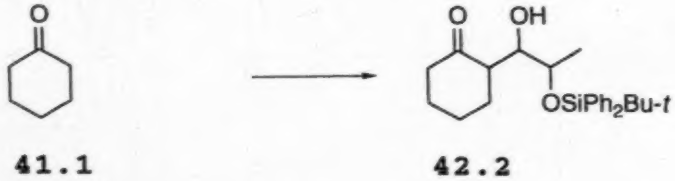
(*E*)-2-(2,2-Diethoxypropylidene)cyclohexanol (41.9).



41.8 **41.9**

Li(t-BuO)$_3$AlH (1.0 M in THF, 0.095 mL, 0.095 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone **41.8** (18.0 mg, 0.0795 mmol) in THF (1.5 mL), and stirring was continued for 20 min. The mixture was quenched with brine (20 drops), diluted with Et_2O (20 mL), and filtered through a pad of alumina (grade III) (2 x 2 cm), using Et_2O (30 mL) as a rinse. The combined organic filtrates were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over alumina (grade III), using 1:4 EtOAc-Hexane, gave **41.9** (15.1 mg, 83%) as an oil: FTIR (CH_2Cl_2 cast) 3421, 2974, 2932, 2883, 2859, 1686, 1623 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.05-2.05 (m, 17 H), 2.84-2.96 (m, 1 H), 3.35-3.56 (m, 4 H), 3.73-3.83 (m, 1 H), 5.68 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 15.4 (q, two signals overlap), 23.3 (t), 25.0 (q), 26.3 (t), 27.1 (t), 36.9 (t), 55.87 (t), 55.91 (t), 73.0 (d), 100.9 (s), 123.8 (d), 144.6 (s); exact mass *m/z* calcd for $C_{13}H_{24}O_3$ 228.1726, found 228.1719.

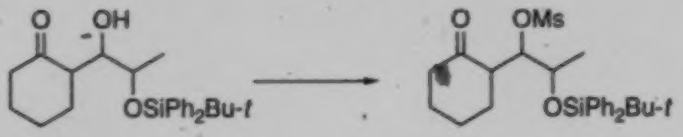
2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-hydroxypropyl]cyclohexanone (42.2).



A solution of cyclohexanone (0.90 mL, 8.67 mmol) in THF (15 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [generated by dropwise addition of BuLi (2.5 M, 3.9 mL, 9.7 mmol) to *i*-Pr_2NH (1.4 mL, 10.0 mmol) in THF (60 mL) at 0 °C, followed, after 15 min, by cooling to -78 °C]. After 1 h, aldehyde **42.1**[53] (1.384 g, 4.428 mmol) in THF (20 mL) was added quickly. Stirring was continued for 50 min at -78 °C, and the reaction was quenched with saturated aqueous NH_4Cl (9 mL). The cooling bath was removed and stirring was continued until the mixture had reached room temperature. The mixture was diluted with Et_2O (150 mL), washed with water and brine, dried ($MgSO_4$), and evaporated.

Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:6 EtOAc-hexane, gave alcohols **42.2** as a mixture of three diastereoisomers (one diastereoisomer being the major component) (^{13}C NMR, three signals at 69.2, 69.8, 70.8 ppm, representing three diastereoisomers, for example) (1.669 g, 92%): FTIR (CH_2Cl_2, cast) 3520, 2932, 2857, 1696 cm^{-1}; exact mass (HR electrospray) *m/z* calcd for $C_{25}H_{34}NaO_3Si$ 433.2175, found 433.2168.

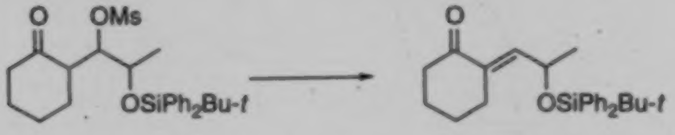
(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]propylidene]cyclohexanone (42.3). (a) Methanesulfonic Acid 2-[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]-1-(2-oxocyclohexyl)propyl Ester.



42.2 --

$MeSO_2Cl$ (0.96 mL, 12.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **42.2** (1.6334 g, 3.9778 mmol) and Et_3N (2.8 mL, 20 mmol) in CH_2Cl_2 (64 mL). The cooling bath was left in place, but was not recharged. Stirring was continued for 6 h, the solution was quenched with saturated aqueous $NaHCO_3$ (15 mL), diluted with Et_2O (200 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (4 x 3 cm) of silica gel, using Et_2O (100 mL) as a rinse. Evaporation of the filtrate gave the crude mesylates (1.5785 g, 81%), which were used immediately for next step.

(b) (*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]cyclohexanone (42.3).

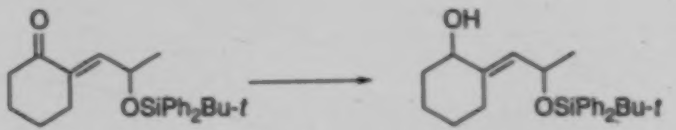


-- **42.3**

DBU (1.0 mL, 6.7 mmol) was added dropwise to a stirred solution of the above mesylates (1.5785 g, 3.2298 mmol) in THF (26 mL). After 1 h, the mixture was diluted with Et_2O (200 mL) and washed with water, 5% hydrochloric acid, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:10 EtOAc-hexane, gave enone **42.3** (0.9631 g, 76%): FTIR (CH_2Cl_2 cast) 2931, 2889, 2857, 1691, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.26-1.40 (m, 1 H), 1.50-1.62 (m, 1 H), 1.62-1.82 (m, 2 H), 2.00 (ddd, *J* = 7.0, 6.0, 2.0 Hz, 2 H), 2.26 (ddd, *J* = 17.0, 9.0, 5.6 Hz, 1 H), 2.40 (dt, *J* = 17.0, 5.0 Hz, 1 H), 4.52 (dq, *J* = 8.0, 6.3 Hz, 1 H), 6.54 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.62-7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (two signals overlap in this spectrum) 19.2 (s), 23.0 (q), 23.3 (t), 23.4 (t), 26.7 (t), 26.9 (q), 66.0 (d), 127.5 (d), 127.6 (d), 129.6 (d), 129.7 (d), 133.8 (s), 133.9 (s), 134.1 (s), 135.8 (d), 135.9 (d), 141.5 (d), 201.3 (s); exact mass (HR

electrospray) *m/z* calcd for $C_{25}H_{32}NaO_2Si$ 415.2069, found 415.2073. The *E* geometry was assigned by comparison of the chemical shift of the vinyl hydrogen with values reported for the model compounds (*E*)-2-ethylidenecyclohexanone[55] and (*Z*)-2-ethylidenecyclohexanone.[55]

(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]propylidene]cyclohexanol (42.4a,b).

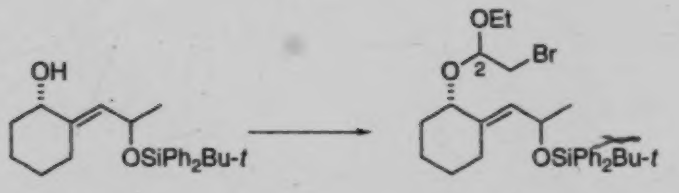


42.3 **42.4a,b**

$NaBH_4$ (6.9 mg, 0.18 mmol) was added in small portions to a stirred and cooled (0 °C) solution of enone **42.3** (44.6 mg, 0.114 mmol) and $CeCl_3.7H_2O$ (65 mg, 0.17 mmol) in MeOH (1.5 mL) and THF (0.4 mL). After 1 h, the mixture was quenched with saturated aqueous NH_4Cl (0.3 mL), diluted with Et_2O (20 mL), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (20 mL) as a rinse. The organic filtrate was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:10 EtOAc-hexane, gave alcohols **42.4** as two separable diastereoisomers, **42.4a** (less polar)(29.2 mg, 65%) and **42.4b** (more polar) (7.3 mg, 16%). Diastereoisomer **42.4a** had: FTIR (CH_2Cl_2 cast) 3387, 2931, 2892, 2857, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, *J* = 4.3 Hz, 1 H), 1.05 (s, 9 H), 1.10-1.50 (m, 7 H, including a doublet at δ 1.20, *J* = 6.2 Hz), 1.55-1.78 (m, 3 H), 1.80-2.05 (m, 1 H), 3.81-3.91 (m, 1 H), 4.65 (dq, *J* = 8.3, 6.2 Hz, 1 H), 5.37 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.65-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.2 (s), 22.6 (t), 25.0 (q), 26.0 (t), 26.7 (t), 27.0 (q), 35.6 (t), 66.1 (d), 73.1 (d), 126.5 (d), 127.4 (d), 127.6 (d), 129.46 (d), 129.54 (d), 134.6 (s), 134.9 (s), 135.9 (d), 136.1 (d), 139.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_{25}H_{34}NaO_2Si$ 417.2226, found 417.2229.

Diastereoisomer **42.4b** had: FTIR (CH_2Cl_2 cast) 3358, 2931, 2892, 2857, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 9 H), 1.11-1.61 (m, including a doublet at δ 1.21, *J* = 6.2 Hz, 9 H in all), 1.61-1.88 (m, 2 H), 1.95-2.15 (m, 1 H), 3.84-3.95 (m, 1 H), 4.65 (dq, *J* = 8.3, 6.2 Hz, 1 H), 5.44 (d, *J* = 8.3 Hz, 1 H), 7.27-7.50 (m, 6 H), 7.60-7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (s), 22.8 (t), 25.0 (q), 26.3 (t), 26.9 (t), 27.0 (q), 35.7 (t), 65.9 (d), 73.2 (d), 126.1 (d), 127.3 (d), 127.5 (d), 129.4 (d), 129.5 (d), 134.6 (s), 134.7 (s), 135.8 (d), 135.9 (d), 139.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{25}H_{34}NaO_2Si$ 417.2226, found 417.2223.

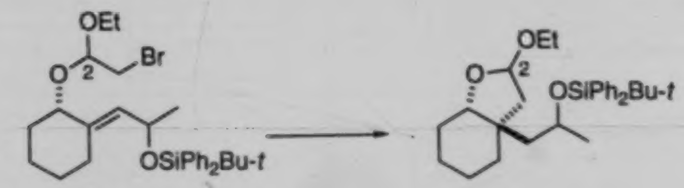
(*E*)-[[1-[2-(2-Bromo-1-ethoxyethoxy)cyclohexylidene]-2-propyl]oxy](1,1-dimethylethyl)diphenylsilane (42.5).



42.4a **42.5**

NBS (0.7472 g, 4.198 mmol), dry CH_2Cl_2 (18.5 mL) and ethyl vinyl ether (1.35 mL, 14.1 mmol) were mixed under Ar in a 50-mL round-bottomed flask until a homogeneous solution was obtained. This solution was added dropwise by syringe to a stirred and cooled (0 °C) solution of alcohol **42.4a** (i.e. major diastereoisomer) (0.5523 g, 1.400 mmol) in CH_2Cl_2 (7.5 mL), the reaction mixture being protected from light by aluminum foil. The cold bath was left in place, and stirring was continued for 25 h. The mixture was then diluted with CH_2Cl_2 (100 mL), washed with 10% aqueous $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:25 EtOAc-hexane, gave bromoacetals **42.5** (0.4925 g, 66%) as a mixture [1:1 (^{1}H NMR)] of two diastereoisomers: FTIR (CH_2Cl_2 cast) 2965, 2931, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.8-1.10 (m, 4 H), 1.10-1.56 (m, 15 H), 1.56-2.10 (m, 4 H), 3.10-3.60 (m, 4 H), 3.70-3.78 (m, 0.5 H), 3.98-4.07 (m, 0.5 H), 4.52-4.62 (m, 1 H), 4.62-4.78 (m, 1 H), 5.63 (d, *J* = 8.2 Hz, 0.5 H), 5.67 (d, *J* = 8.3 Hz, 0.5 H), 7.16-7.35 (m, 6 H), 7.72-7.88 (m, 4 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.5 (q), 15.6 (q), 19.4 (s), 21.5 (t), 22.2 (t), 25.3 (q), 26.2 (t), 27.2 (q), 27.4 (t), 27.7 (t), 32.7 (t), 32.9 (t), 34.0 (t), 34.3 (t), 61.8 (t), 62.0 (t), 66.3 (d), 66.4 (d), 77.4 (d), 78.1 (d), 98.9 (d), 100.6 (d), 127.9 (d), 128.0 (d), 129.0 (d), 129.9 (d), 130.0 (d), 131.5 (d), 134.56 (s), 134.61 (s), 134.96 (s), 134.99 (s), 136.2 (d), 136.3 (d), 136.8 (s), 137.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{29}H_{41}{}^{79}BrNaO_3Si$ 567.1906, found 567.1912.

(3a*R,7a*S**)-3a-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propyl]-2-ethoxyoctahydrobenzofuran (43.1).**

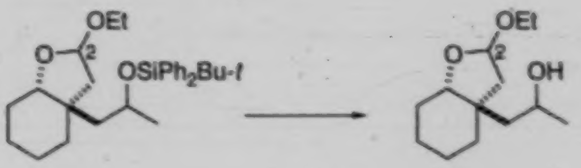


42.5 **43.1**

Bu_3SnH (0.37 mL, 1.37 mmol) and AIBN (21 mg, 0.13 mmol) were added to a stirred solution of bromoacetals **42.5** (0.3952 g, 0.7243 mmol) in PhMe (50 mL). The flask was then lowered into a preheated oil bath set at 115 °C (continued stirring). After 1.5 h, the mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:30 EtOAc-hexane, gave acetals **43.1** (0.3100 g, 92%) as a mixture [ca 4:3 (^{1}H NMR)] of two diastereoisomers, differing in stereochemistry at C(2): FTIR (CH_2Cl_2 cast) 2931, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.80-1.80 (m, 24 H), 1.85-2.15 (m, 3 H), 3.30-3.45 (m, 1 H), 3.45-3.96 (m, 2 H), 3.96-4.12 (m, 1

H), 5.05-5.18 (two t, J = 5.1 Hz, J' = 4.5 Hz, 1 H), 7.15-7.28 (m, 6 H), 7.63-7.9 (m, 4 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.4 (q), 15.5 (q), 16.8 (s), 19.2 (s), 20.2 (t), 21.3 (t), 21.6 (t), 21.7 (t), 25.2 (t), 25.5 (q), 25.8 (q), 27.0 (q), 27.5 (t), 30.5 (t), 31.8 (t), 41.1 (s), 42.1 (s), 43.4 (t), 44.8 (t), 46.2 (t), 47.7 (t), 63.2 (t), 63.5 (t), 68.1 (d), 79.4 (d), 82.8 (d), 103.0 (d), 103.8 (d), 127.8 (d), 128.0 (d), 129.5 (d), 129.7 (d), 134.2 (s), 135.2 (s), 136.0 (d), 136.1 (d); exact mass (HR electrospray) *m/z* calcd for $C_{29}H_{42}NaO_3Si$ 489.2801, found 489.2806.

1-[(3a*R,7a*S**)-2-Ethoxyoctahydrobenzofuran-3a-yl]-2-propanol (43.2).**

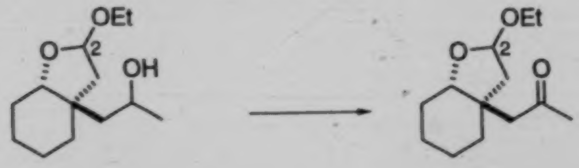


43.1 **43.2**

Bu_4NF (1.0 M in THF, 3.5 mL, 3.5 mmol) was added dropwise to a stirred solution of acetals **43.1** (0.4090 g, 0.8763 mmol) in THF (30 mL). The stirred mixture was warmed to 45 °C for 150 min, cooled to room temperature, diluted with Et_2O (120 mL), and washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 1:4 EtOAc-hexane, gave alcohols **43.2** (185 mg, 92%) as a chromatographically

inseparable mixture [ca 4:3 (^{1}H NMR)] of two diastereoisomers, differing in stereochemistry at C(2): FTIR (CH_2Cl_2, cast) 3443, 2969, 2931, 2861 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.92-1.50 (m, 13 H), 1.50-1.75 (m, 1.5 H), 1.77-2.12 (m, 4 H), 2.63 (br s, 0.5 H), 3.25-3.45 (m, 1 H), 3.55-3.95 (m, 3 H), 5.05-5.20 (m, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.3 (q), 15.4 (q), 20.3 (t), 21.5 (t), 21.7 (t), 21.9 (t), 25.2 (t), 25.4 (q), 25.6 (q), 28.1 (t), 31.27 (t), 31.33 (t), 42.0 (s), 42.3 (s), 42.6 (t), 43.8 (t), 47.4 (t), 63.3 (t), 63.6 (t), 64.2 (d), 64.3 (d), 79.7 (d), 82.8 (d), 103.2 (d), 104.4 (d); exact mass *m/z* calcd for $C_{13}H_{24}O_3$ 228.1726, found 228.1729.

1-[(3a*R**,7a*R**)-2-Ethoxyoctahydrobenzofuran-3a-yl]-2-propanone (43.3a,b).

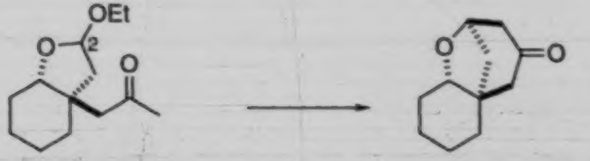


43.2 **43.3a,b**

A solution of alcohols **43.2** (26.8 mg, 0.117 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred mixture of PCC (38.0 mg, 0.176 mmol), powdered 4 Å molecular sieves (150 mg) and CH_2Cl_2 (1 mL). After 3 h, the mixture was diluted with Et_2O (10 mL), and filtered through a pad (2 x 1.5 cm) of silica gel, using Et_2O (20 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 15 cm), using 1:9 EtOAc-hexane, gave ketones **43.3** as two separable diastereoisomers, **43.3a** (less polar) (11.0 mg, 41%) and **43.3b** (more polar) (8.2 mg, 31%), differing in stereochemistry at C(2). Diastereoisomer **43.3a** had: FTIR (CH_2Cl_2, cast) 2974, 2933, 2862, 1712 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.96-1.24 (m, 1 H), 1.17-1.24 (t, *J* = 7.0 Hz, 3 H), 1.24-1.45 (m, 4 H), 1.55-1.72 (m, 1 H), 1.65 (s, 3 H), 1.72-1.85 (m, 2 H), 1.92 (dd, *J* = 13.6, 4.0 Hz, 1 H), 1.95-2.07 (m, 1 H), 2.35 (d, *J* = 16.0 Hz, 1 H), 2.42 (dd, *J* = 13.6, 6.0 Hz, 1 H), 3.41 (dq, *J* = 9.6, 7.0 Hz, 1 H), 3.72 (t, *J* = 3.0 Hz, 1 H), 3.93 (dq, *J* = 9.6, 7.0 Hz, 1 H), 5.15 (dd, *J* = 6.0, 4.0 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.3 (q), 20.1 (t), 21.6 (t), 25.5 (t), 30.3 (t), 30.7 (q), 41.5 (s), 46.3 (t), 46.8 (t), 63.4 (t), 79.5 (d), 103.0 (d), 205.0 (s); exact mass *m/z* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1567.

Diastereoisomer **43.3b** had: FTIR (CH_2Cl_2 cast) 2973, 2931, 2862, 1716 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 1.09-1.31 (m, 2 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 1.31-1.45 (m, 1 H), 1.45-1.60 (m, 2 H), 1.60-1.72 (m, 1 H), 1.70 (s, 3 H), 1.84 (d, *J* = 16.0 Hz, 1 H), 1.90-2.17 (m, 3 H), 2.19-2.29 (m, 2 H), 3.41 (dq, *J* = 10.0, 7.0 Hz, 1 H), 3.58 (t, *J* = 5 Hz, 1 H), 3.94 (dq, *J* = 10.0, 7.0 Hz, 1 H), 5.11 (dd, *J* = 6.5, 3.0 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.4 (q), 21.5 (t), 21.7 (t), 28.0 (t), 30.4 (t), 31.1 (q), 41.7 (s), 43.5 (t), 49.1 (t), 63.6 (t), 81.8 (d), 103.9 (d), 205.4 (s); exact mass *m/z* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1569.

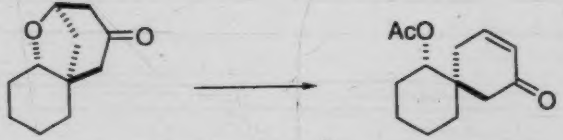
(1*R**,6*R**,8*S**)-7-Oxatricyclo[6.3.1.0^{1,6}]dodecan-10-one (43.4).



43.3a,b **43.4**

A solution of ketones **43.3a** and **43.3b** (ca 4:3) (0.1359 g, 0.6004 mmol) in a mixture of 3 M hydrochloric acid (30 mL) and THF (6 mL) was refluxed (85 °C) for 24 h, cooled to room temperature, and extracted with EtOAc (100 mL). The aqueous layer was washed with EtOAc (2 x 50 mL), and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave tricyclic ketone **43.4** (80.1 mg, 74%) as a solid: FTIR (CH_2Cl_2 cast) 2934, 2861, 1716 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.64-0.90 (m, 3 H), 0.91-1.10 (m, 2 H), 1.17-1.27 (m, 1 H), 1.29-1.45 (m, 2 H), 1.73-1.84 (m, 1 H), 1.84 (t, J = 16.8 Hz, 2 H), 1.99-2.07 (m, 1 H), 2.16 (dt, J = 16.8, 2.6 Hz, 1 H), 2.60-2.71 (m, 1 H), 3.49 (dd, J = 10.4, 4.4 Hz, 1 H), 4.15-4.21 (m, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 21.4 (t), 23.2 (t), 32.0 (t), 32.5 (t), 36.1 (t), 42.1 (s), 49.3 (t), 56.4 (t), 73.4 (d), 82.1 (d), 207.1 (s); exact mass *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1150.

Acetic Acid (1*R**,6*R**)-10-Oxospiro[5.5]undec-8-en-1-yl Ester (43.5).

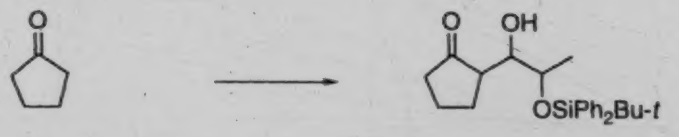


43.4 **43.5**

A solution of ketone **43.4** (50.2 mg, 0.279 mmol), TsOH.H_2O (47 mg, 0.27 mmol), and Ac_2O (0.40 mL, 4.2 mmol) in PhH (55 mL) was heated at 85 °C for 40 h, cooled, and evaporated. The residue was diluted with Et_2O (100 mL), washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave spiro enone **43.5** (42.5 mg, 69%): FTIR (CH_2Cl_2 cast) 3035, 2938, 2864, 1734, 1680, 1621 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.85-1.14 (m, 4 H), 1.24-1.42 (m, 2 H), 1.45-1.55 (m, 1 H), 1.55-1.65 (m, 1 H), 1.68 (s, 3 H), 1.82 (dt, J = 19.0, 1.5 Hz, 1 H), 2.11 (dt, J = 19.0, 3.0 Hz, 1 H), 2.15 (d, J = 15.4 Hz, 1 H), 2.37 (d, J = 15.4 Hz, 1 H), 4.63 (dd, J = 9.0, 4.0 Hz, 1 H), 5.96-6.02 (m, 1 H), 6.16 (ddd, J = 9.6, 5.2, 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.6 (t), 21.1 (q), 23.0 (t), 26.3 (t), 30.1 (t), 32.2 (t), 40.3 (s), 47.6 (t), 77.0 (d), 128.9 (d), 147.5 (d), 170.2 (s), 198.8 (s); exact mass *m/z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1258.

2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-

hydroxypropyl]cyclopentanone (44.2a,b).

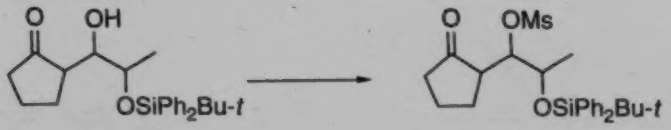


44.1 **44.2a,b**

A solution of cyclopentanone (1.72 mL, 19.5 mmol) in THF (34 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (21.4 mmol) in THF (140 mL). After 1 h, aldehyde **42.1**[53] (3.0450 g, 9.7446 mmol) in THF (48 mL) was added quickly. Stirring was continued for 1 h at -78 °C and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The cooling bath was removed and stirring was continued until the mixture had reached room temperature. The mixture was diluted with Et_2O (100 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:10 EtOAc-hexane, gave aldols **44.2** as two fractions, **44.2a** (more polar) (2.2118 g, 57%) and **44.2b** (less polar) (0.7671 g, 20%), each of which contained trace impurities (^1H NMR). Fraction **44.2a** had: FTIR (CH_2Cl_2 cast) 3491, 2961, 2931, 2886, 2857, 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97-2.30 (m, 7 H), 1.10 (s, 9 H), 1.12 (d, J = 7.0 Hz, 3 H), 3.62 (dt, J = 8.5, 2.8 Hz, 1 H), 3.77 (dd, J = 2.5, 0.6 Hz, 1 H), 3.89 (dq, J = 6.3, 2.8 Hz, 1 H), 7.35-7.47 (m, 6 H), 7.69-7.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.0 (q), 19.1 (s), 20.4 (t), 26.5 (t), 26.9 (q), 38.0 (t), 50.2 (d), 71.0 (d), 75.8 (d), 127.4 (d), 127.44 (d), 129.47 (d), 129.5 (d), 133.8 (s), 134.1 (s), 135.7 (d), 222.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{24}H_{32}NaO_3Si$ 419.2018, found 419.2020.

Fraction **44.2b** had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96-2.42 (m, 10 H), 1.08 (s, 9 H), 3.66 (ddd, J = 8.0, 4.0, 2.0 Hz, 1 H), 4.01 (dq, J = 7.5, 3.6 Hz, 1 H), 4.07 (d, J = 2.0 Hz, 1 H), 7.35-7.50 (m, 6 H), 7.65-7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.7 (q), 19.3 (s), 21.0 (t), 27.1 (q), 27.2 (t), 78.7 (t), 50.1 (d), 70.9 (d), 76.1 (d), 127.5 (d), 127.8 (d), 129.7 (d), 129.8 (d), 133.6 (s), 134.3 (s), 135.75 (d), 135.8 (d), 136.0 (d), 223.7 (s).

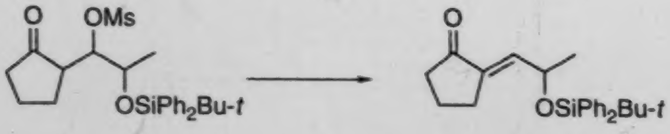
(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]cyclopentanone (44.3) from 44.2a (major diastereoisomer of 44.2). (a) Methanesulfonic Acid 2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-(2-oxocyclopentyl)propyl Ester.



44.2a --

MeSO$_2$Cl (0.44 mL, 5.7 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **44.2a** (i.e. major diastereoisomer of **44.2**) (0.7360 g, 1.8557 mmol) and Et$_3$N (1.3 mL, 9.3 mmol) in CH$_2$Cl$_2$ (35 mL). The cooling bath was left in place, but was not recharged. Stirring was continued for 4 h, the solution was quenched with saturated aqueous $NaHCO_3$ (7 mL), diluted with Et_2O (100 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (50 mL) as a rinse. Evaporation of the filtrate gave the crude mesylate (0.8280 g, 94%), which was used immediately for next step.

(b) (*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]cyclopentanone (44.3).

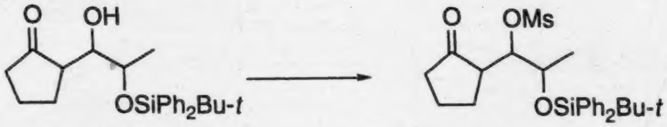


--   **44.3**

DBU (0.54 mL, 3.6 mmol) was added dropwise to a stirred solution of the above mesylates (0.8280 g, 1.744 mmol) in THF (17 mL). After 1 h, the mixture was diluted with Et_2O (100 mL), washed successively with water, 5% hydrochloric acid, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:10 EtOAc-hexane, gave enone **44.3** (0.5850 g, 89%): FTIR (CH_2Cl_2 cast) 2963, 2930, 2891, 2857, 1722, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9 H), 1.25 (d, J = 6.4 Hz, 3 H), 1.50-1.70 (m, 1 H), 1.70-1.80 (m, 1 H), 1.92-2.06 (m, 1 H), 2.12-2.30 (m, 3 H), 4.44 (dq, J = 7.6, 6.4 Hz, 1 H), 6.50 (dt, J = 8.2, 2.7 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.62-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.1 (s), 19.8 (t), 23.1 (q), 26.4 (t), 26.9 (q), 38.1 (t), 67.8 (d), 127.5 (d), 127.6

(d), 129.66 (d), 129.70 (d), 133.8 (s), 134.0 (s), 134.6 (s), 135.8 (d), 135.9 (d), 138.0 (d), 207.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_{24}H_{30}NaO_2Si$ 401.1913, found 401.1916. The *E* geometry was assigned on the basis of the chemical shift arguments used for **42.3**.

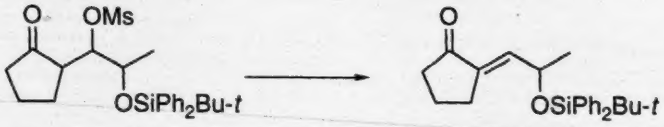
(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]cyclopentanone (44.3) from 44.2b (minor diastereoisomer of 44.2). (a) Methanesulfonic Acid 2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-(2-oxocyclopentyl)propyl Ester.



44.2b --

$MeSO_2Cl$ (0.45 mL, 5.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **44.2b** (i.e. minor diastereoisomer of **44.2**) (0.7485 g, 1.887 mmol) and Et_3N (1.3 mL, 9.3 mmol) in CH_2Cl_2 (36 mL). The cooling bath was left in place, but was not recharged. Stirring was continued for 6 h, the solution was quenched with saturated aqueous $NaHCO_3$ (7 mL), diluted with Et_2O (100 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (50 mL) as a rinse. Evaporation of the filtrate gave the crude mesylate (0.4875 g, 54%), which was used immediately for next step.

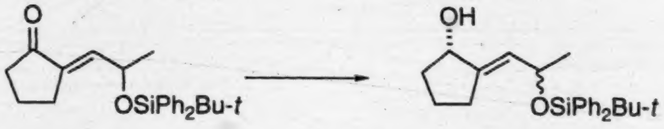
(b) (*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]cyclopentanone (44.3).



--   **44.3**

DBU (0.32 mL, 2.1 mmol) was added dropwise to a stirred solution of the above mesylates (0.4875 g, 1.027 mmol) in THF (10 mL). After 45 min, the mixture was diluted with Et_2O (80 mL), washed successively with water, 5% hydrochloric acid, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:15 EtOAc-hexane, gave enone **44.3** (0.2560 g, 66%), spectroscopically identical with material obtained from the major diastereoisomer series.

(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]propylidene]cyclopentanol (44.4a,b).



44.3   **44.4a,b**

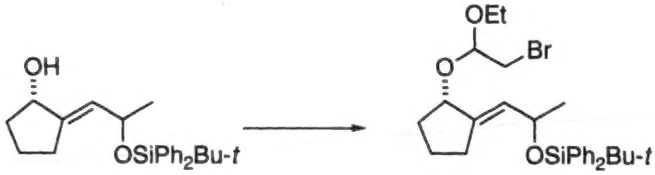
$NaBH_4$ (0.3680 g, 9.725 mmol) was added in small portions to a stirred and cooled (0 °C) solution of enone **44.3** (2.4240 g, 6.4027 mmol) and $CeCl_3.7H_2O$ (3.4210 g, 9.1817 mmol) in MeOH

(74 mL). After 1 h, the mixture was quenched with saturated aqueous NH_4Cl (14 mL), diluted with Et_2O (200 mL), and filtered through a pad (3 x 4 cm) of silica gel, using Et_2O (100 mL) as a rinse. The organic filtrate was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:8 EtOAc-hexane, gave alcohols **44.4** as two separable diastereoisomers, **44.4a** (less polar) (1.3555 g, 55%) and **44.4b** (more polar) (1.0530 g, 43%). Diastereoisomer **44.4a** had: FTIR (CH_2Cl_2 cast) 3432, 2962, 2930, 2891, 2857 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.64 (d, J = 6.0 Hz, 1 H), 1.07 (s, 9 H), 1.18-1.58 (m, 3 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.63-1.84 (m, 3 H), 4.15 (q, J = 6.0 Hz, 1 H), 4.43 (dq, J = 8.0, 6.0 Hz, 1 H), 5.47 (dq, J = 8.0, 2.0 Hz, 1 H), 7.33-7.48 (m, 6 H), 7.66-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.1 (s), 21.5 (t), 23.9 (q), 26.5 (t), 27.0 (q), 35.1 (t), 68.1 (d), 75.2 (d), 127.4 (d), 127.6 (d), 128.3 (d), 129.6 (d), 134.3 (s), 135.0 (s), 135.8 (d), 136.0 (d), 144.3 (s); exact mass (HR electrospray) m/z calcd for $C_{24}H_{32}NaO_2Si$ 403.2069, found 403.2070.

Diastereoisomer **44.4b** had: FTIR (CH_2Cl_2 cast) 3340, 2962, 2930, 2892, 2857 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 9 H), 1.26 (d, J = 6.0 Hz, 3 H), 1.30-1.43 (m, 1 H), 1.46-1.60 (m, 3 H), 1.62-1.75 (m, 2 H), 1.91-2.03 (m, 1 H), 4.25 (s, 1 H), 4.39 (dq, J = 8.0, 6.0 Hz, 1 H), 5.61 (dd, J = 8.0, 1.0 Hz, 1 H), 7.32-7.48 (m, 6 H), 7.66-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.2 (s), 22.1 (t), 24.1 (q), 26.3

(t), 27.0 (q), 35.0 (t), 68.0 (d), 75.6 (d), 127.3 (d), 127.5 (d), 128.7 (d), 129.4 (d), 129.5 (d), 134.46 (s), 134.50 (s), 135.86 (d), 135.93 (d), 144.4 (s); exact mass (HR electrospray) *m/z* calcd for $C_{24}H_{32}NaO_2Si$ 403.2069, found 403.2072.

(*E*)-[[1-[2-(2-Bromo-1-ethoxyethoxy)cyclopentylidene]-2-propyl]oxy](1,1-dimethylethyl)diphenylsilane (44.5).

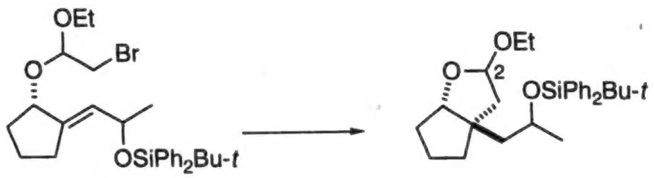


44.4a **44.5**

NBS (1.8235 g, 10.245 mmol), dry CH_2Cl_2 (46 mL) and ethyl vinyl ether (3.3 mL, 34 mmol) were mixed under Ar until a homogeneous solution was obtained. This solution was added dropwise by syringe to a stirred and cooled (0 °C) solution of alcohol **44.4a** (i.e. major diastereoisomer) (1.3000 g, 3.4155 mmol) in CH_2Cl_2 (18 mL), the reaction mixture being protected from light by aluminum foil. The cold bath was left in place, and stirring was continued for 18 h. The mixture was then diluted with CH_2Cl_2 (200 mL), washed with 10% aqueous $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:40 EtOAc-hexane, gave bromoacetals

44.5 (1.1870 g, 65%) as a chromatographically inseparable mixture [ca 1:1 (^{1}H NMR) of two diastereoisomers: FTIR (CH_2Cl_2 cast) 2965, 2930, 2891, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 1.12 (t, J = 7.0 Hz, 1.5 H), 1.13 (t, J = 7.0 Hz, 1.5 H), 1.23 (s, 4.5 H), 1.24 (s, 4.5 H), 1.30 (d, J = 6.2 Hz, 2 H), 1.32 (d, J = 6.2 Hz, 2 H), 1.38-1.58 (m, 2 H), 1.58-1.80 (m, 3 H), 3.15-3.31 (m, 2 H), 3.31-3.42 (m, 1 H), 3.42-3.53 (m, 1 H), 4.12-4.20 (m, 1 H), 4.44-4.58 (m, 1 H), 4.70 (t, J = 5.5 Hz, 0.5 H), 4.77 (t, J = 5.5 Hz, 0.5 H), 5.85 (d, J = 8.5 Hz, 0.5 H), 5.90 (dq, J = 8.5, 2.0 Hz, 0.5 H), 7.15-7.30 (m, 6 H), 7.75-7.85 (m, 4 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.2 (q), 19.2 (s), 21.6 (t), 22.0 (t), 23.9 (q), 24.0 (q), 25.8 (t), 26.3 (t), 26.8 (q), 27.0 (q), 32.1 (t), 32.2 (t), 32.3 (t), 33.4 (t), 60.7 (t), 60.8 (t), 68.2 (d), 79.0 (d), 79.8 (d), 99.6 (d), 100.1 (d), 127.56 (d), 127.6 (d), 129.3 (d), 129.5 (d), 129.59 (d), 129.63 (d), 130.3 (d), 134.3 (s), 134.4 (s), 134.6 (s), 134.7 (s), 136.0 (d), 136.1 (d), 136.2 (d), 140.4 (s), 141.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{39}{}^{79}BrNaO_3Si$ 553.1750, found 553.1751.

(3a*R,7a*S**)-3a-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propyl]-2-ethoxyhexahydrocyclopenta[b]furan (44.6).**

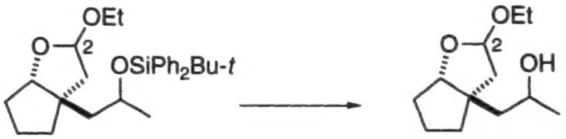


44.5 **44.6**

Bu_3SnH (0.57 mL, 2.11 mmol) and AIBN (33 mg, 0.20 mmol) were added to a stirred solution of bromoacetals **44.5** (0.6860 g, 1.290 mmol) in PhMe (90 mL). The flask was then lowered into a preheated oil bath set at 115 °C (continued stirring). After 1 h, the mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:40 EtOAc-hexane, gave acetals **44.6** (0.5290 g, 90%) as a chromatographically inseparable mixture [ca 1:1 (^{1}H NMR)] of two diastereoisomers, differing in stereochemistry at C(2): FTIR (CH_2Cl_2 cast) 2961, 2931, 2898, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.10 (d, J = 6.0 Hz, 1.5 H), 1.11 (d, J = 6.0 Hz, 1.5 H), 1.16 (t, J = 7.0 Hz, 1.5 H), 1.17 (t, J = 7.0, 1.5 H), 1.19-2.24 (m, 9 H), 1.22 (s, 4.5 H), 1.25 (s, 4.5 H), 2.43 (d, J = 13.0 Hz, 0.5 H), 2.51 (dd, J = 14.0, 6.0 Hz, 0.5 H), 3.30-3.41 (m, 1 H), 3.74-3.90 (m, 1 H), 4.04 (sextet, J = 6.0 Hz, 0.5 H), 4.14 (sextet, J = 6.0 Hz, 0.5 H), 4.19 (d, J = 5.0 Hz, 1 H), 5.06 (dd, J = 5.6, 2.0 Hz, 0.5 H), 5.13 (d, J = 5.0 Hz, 0.5 H), 7.15-7.30 (m, 6 H), 7.75-7.90 (m, 4 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.2 (q), 15.3 (q), 19.15 (s), 19.20 (s), 24.3 (t) 24.5 (t), 25.2 (q), 25.4 (q), 27.0 (q), 27.1 (q), 32.8 (t), 34.0 (t), 38.8 (t), 39.5 (t), 46.0 (t), 46.1

(t), 49.9 (s or t), 50.9 (s or t), 51.29 (s or t), 51.35 (s or t), 62.0 (t), 62.7 (t), 68.9 (d), 69.1 (d), 90.7 (d), 92.8 (d), 104.7 (d), 105.2 (d), 127.6 (d), 127.7 (d), 129.5 (d), 129.6 (d), 129.65 (d), 129.7 (d), 134.3 (s), 134.4 (s), 135.0 (s), 135.3 (s), 136.0 (d), 136.07 (d), 136.12 (d); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{40}NaO_3Si$ 475.2644, found 475.2649.

1-[(3a*R,7a*S**)-2-Ethoxyhexahydrocyclopenta[b]-furan-3a-yl]-2-propanol (44.7a,b).**

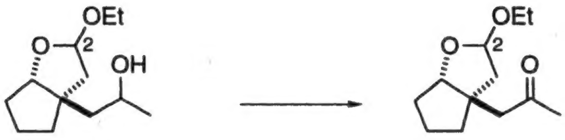


44.6 **44.7a,b**

Bu_4NF (1.0 M in THF, 2.5 mL, 2.5 mmol) was added dropwise to a stirred solution of acetals **44.6** (0.4750 g, 1.049 mmol) in THF (44 mL). The stirred mixture was warmed to 45 °C for 4 h, cooled to room temperature, diluted with Et_2O (200 mL), and washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 1:6 EtOAc-hexane, gave alcohols **44.7** as two diastereoisomers, **44.7a** (more polar) (99.8 mg, 44%) and **44.7b** (less polar) (88.0 mg, 39%), differing in stereochemistry at C(2). Diastereoisomer **44.7a** had: FTIR (CH_2Cl_2 cast) 3432, 2967, 2908 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.01 (d, J = 6.2 Hz, 3 H), 1.15-1.44 (m, 4 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 1.51-1.65 (m, 2 H), 1.87-1.96 (m, 1 H), 1.96-2.06 (m, 1 H), 2.08 (dd, *J* = 13.7, 1.8 Hz, 1 H), 2.17-2.30 (m, 2 H), 3.36 (dq, *J* = 9.4, 7.1 Hz, 1 H), 3.61-3.72 (m, 1 H), 3.89 (dq, *J* = 9.4, 7.1 Hz, 1 H), 4.30 (d, *J* = 4.7 Hz, 1 H), 5.16 (dd, *J* = 5.9, 1.85 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.4 (q), 24.2 (t), 25.5 (q), 34.2 (t), 38.6 (t), 46.3 (t), 49.6 (t), 52.1 (s), 63.0 (t), 65.8 (d), 92.2 (d), 105.8 (d); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{22}NaO_3$ 237.1467, found 237.1467.

Diastereoisomer **44.7b** had: FTIR (CH_2Cl_2 cast) 3455, 2960 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 1.10-1.25 (m, 1 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H), 1.29-1.52 (m, 4 H), 1.52-1.74 (m, 3 H), 1.92-2.03 (m, 1 H), 2.34 (d, *J* = 13.8 Hz, 1 H), 3.28 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.31 (s, 1 H), 3.75 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.92-4.08 (m, 1 H), 4.68 (d, *J* = 5.0 Hz, 1 H), 5.03 (d, *J* = 5.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.2 (q), 24.2 (t), 24.7 (q), 33.6 (t), 43.1 (t), 44.9 (t), 48.6 (t), 51.1 (s), 62.6 (t), 65.0 (d), 89.3 (d), 105.0 (d); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{22}NaO_3$ 237.1467, found 237.1465.

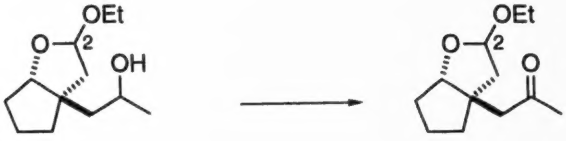
1-[(3a*R,7a*R**)-2-Ethoxyhexahydrocyclopenta[b]-furan-3a-yl]-2-propanone (44.8) from 44.7a (major diastereoisomer of 44.7).**



44.7a **44.8**

A solution of alcohol **44.7a** (i.e. major diastereoisomer) (87.0 mg, 0.406 mmol) in CH_2Cl_2 (3.6 mL) was added dropwise to a stirred mixture of PCC (0.1326 g, 0.6149 mmol), powdered 4 Å molecular sieves (704 mg) and CH_2Cl_2 (3.6 mL). After 3 h, the mixture was diluted with Et_2O (20 mL), and filtered through a pad (2 x 1.5 cm) of silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave ketone **44.8** (64.0 mg, 74%), whose stereochemistry at C(2) with respect to the quaternary center was not established. Compound **44.8** had: FTIR (CH_2Cl_2 cast) 2971, 2901, 1718 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.17 (t, J = 7.1 Hz, 3 H), 1.32-1.74 (m, 3 H), 1.64 (s, 3 H), 1.92-2.06 (m, 1 H), 1.94 (dd, J = 13.5, 5.8 Hz, 1 H), 2.04 (s, 2 H), 2.06-2.26 (m, 2 H), 2.29 (dd, J = 13.5, 1.8 Hz, 1 H), 3.37 (dq, J = 9.4, 7.1 Hz, 1 H), 3.86 (dq, J = 9.4, 7.1 Hz, 1 H), 4.18 (dd, J = 5.7, 1.3 Hz, 1 H), 5.11 (dd, J = 5.8, 1.8 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 15.4 (q), 24.5 (t), 30.4 (q), 34.5 (t), 39.2 (t), 46.7 (t), 50.6 (s), 53.5 (t), 63.0 (t), 91.4 (d), 105.4 (d), 205.1 (s); exact mass *m/z* calcd for $C_{12}H_{20}O_3$ 212.1413, found 212.1406.

1-[(3a*R**,7a*R**)-2-Ethoxyhexahydrocyclopenta[b]-furan-3a-yl]-2-propanone (44.8′) from 44.7b (minor diastereoisomer of 44.7).

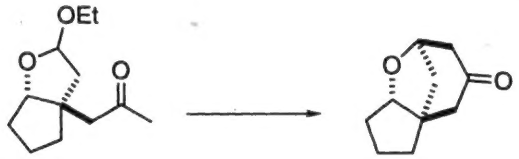


44.7b **44.8′**

A solution of alcohol **44.7b** (i.e. minor diastereoisomer) (74.0 mg, 0.345 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred mixture of PCC (0.1117 g, 0.5180 mmol), powdered 4 Å molecular sieves (500 mg) and CH_2Cl_2 (3 mL). After 3.5 h, the mixture was diluted with Et_2O (20 mL), and filtered through a pad (2 x 1.5 cm) of silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave ketone **44.8′** (0.0521 g, 71%), whose stereochemistry at C(2) with respect to the quaternary center was not established. Compounds **44.8** and **44.8′** have different stereochemistry at C(2). Compound **44.8′** had: FTIR (CH_2Cl_2 cast) 2941, 2902, 2868, 1718 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.14 (t, *J* = 7.1 Hz, 3 H), 1.29-1.39 (m, 1 H), 1.51-1.75 (m, 3 H), 1.64 (s, 3 H), 1.78 (dd, *J* = 13.4, 4.9 Hz, 1 H), 1.81-1.88 (m, 1 H), 1.93-2.00 (m, 1 H), 2.16 (d, *J* = 13.4 Hz, 1 H), 2.41 (d, *J* = 17.8 Hz, 1 H), 2.79 (d, *J* = 17.8 Hz, 1 H), 3.31 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.74 (dq, *J* = 9.6, 7.1 Hz, 1 H), 4.28 (d, *J* = 4.8 Hz, 1 H), 5.06

(d, J = 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.5 (q), 24.5 (t), 30.3 (q), 33.2 (t), 39.7 (t), 46.7 (t), 50.2 (s), 53.2 (t), 62.2 (t), 89.4 (d), 104.5 (d), 205.8 (s); exact mass m/z calcd for $C_{12}H_{20}O_3$ 212.1413, found 212.1412.

(1*R,5*R**,7*S**)-6-Oxatricyclo[5.3.1.0^{1,5}]undecan-9-one (44.9).**

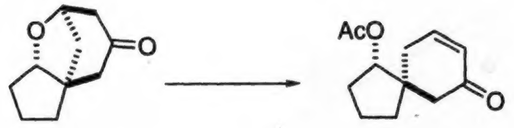


44.8 & **44.8′** **44.9**

A solution of ketones **44.8** and **44.8′** (ca 1:1) (74.0 mg, 0.349 mmol) in a mixture of 3 M hydrochloric acid (17 mL) and THF (3.6 mL) was refluxed (85 °C) for 36 h, cooled to room temperature, and extracted with EtOAc (50 mL). The aqueous layer was washed with EtOAc (2 x 30 mL), and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) using 1:3 EtOAc-hexane gave ketone **44.9** (43 mg, 74%): FTIR (CH_2Cl_2 cast) 2954, 2877, 1715 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 0.84-0.95 (m, 1 H), 1.15 (d, J = 11.2 Hz, 1 H), 1.23-1.45 (m, 2 H), 1.48-1.62 (m, 3 H), 1.64 (ddt, J = 11.2, 5.6, 2.8 Hz, 1 H), 1.80 (dd, J = 17.8, 2.8 Hz, 1 H), 2.16 (d, J = 17 Hz, 1 H), 2.26 (dt, J = 17, 2.0 Hz, 1 H), 2.58 (dq, J = 17.8, 2.0 Hz, 1 H), 3.91 (t,

J = 5.6 Hz, 1 H), 4.17 (dt, J = 5.4, 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.6 (t), 33.2 (t), 34.0 (t), 40.6 (t), 48.3 (t), 50.9 (s), 53.5 (t), 76.4 (d), 88.5 (d), 209.8 (s); exact mass m/z calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

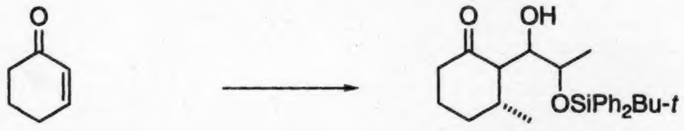
Acetic Acid (1*R,5*R**)-9-Oxospiro[5.4]dec-7-en-1-yl Ester (44.10).**



44.9 **44.10**

A solution of ketone **44.9** (15.2 mg, 0.091 mmol), $TsOH.H_2O$ (15.5 mg, 0.089 mmol), and Ac_2O (0.13 mL, 1.4 mmol) in PhH (18 mL) was heated at 85 °C for 20 h, cooled, and evaporated. The residue was diluted with Et_2O (50 mL), washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 10 cm), using 1:3 EtOAc-hexane, gave enone **44.10** (14.1 mg, 74%): FTIR (CH_2Cl_2 cast) 2958, 2879, 1736, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56-1.86 (m, 5 H), 2.06 (s, 3 H), 2.08-2.19 (m, 1 H), 2.27 (dd, J = 16.0, 1.0 Hz, 1 H), 2.29 (ddt, J = 19.0, 5.0, 1.4 Hz, 1 H), 2.46 (d, J = 16.0 Hz, 1 H), 2.57 (dt, J = 19.0, 2.8 Hz, 1 H), 4.85 (dd, J = 6.4, 4.0 Hz, 1 H), 6.04 (dq, J = 10.0, 2.0 Hz, 1 H), 6.93 (ddd, J = 10.0, 5.0, 3.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.1 (t), 21.1 (q), 29.9 (t), 31.8 (t), 34.4 (t), 47.3 (t), 47.6 (s), 80.6 (d), 129.5 (d), 148.7 (d), 170.4 (s), 198.4 (s); exact mass *m/z* calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1104.

2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-hydroxypropyl]-3-methylcyclohexanone (45.2a,b).

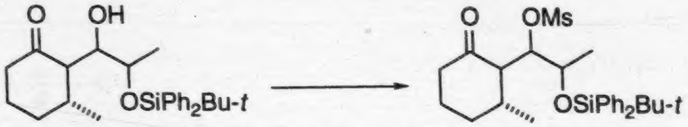


45.1 **45.2a,b**

MeLi (1.4 M in Et_2O, 4.28 mL, 6.0 mmol) was added dropwise to a stirred and cooled (0 °C) suspension of CuI (0.571 g, 3.00 mmol) in Et_2O (30 mL). After 5 min, 2-cyclohexenone (0.145 mL, 1.5 mmol) was added, and stirring was continued at 0 °C for 30 min. $ZnCl_2$ solution (1.0 M in Et_2O, 3.0 mL, 3.0 mmol) was then added, the mixture was cooled to -78 °C, and aldehyde **42.1**[53] (0.94 g, 3.0 mmol) in Et_2O (10 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and saturated aqueous NH_4Cl (20 mL), followed by water (30 mL) were added. The cooling bath was removed, and stirring was continued until the mixture attained room temperature. The mixture was extracted with Et_2O (3 x 50 mL), and the combine organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:10 EtOAc-hexane, gave aldols **45.2** as two fractions, **45.2a** (less polar) (0.4619 g, 72%) and **45.2b** (more polar) (54.7 mg, 8%), each consisting (^{1}H and ^{13}C NMR) of a single diastereoisomer. Diastereoisomer **45.2a** had: FTIR (CH_2Cl_2 cast) 3515, 2957, 2932, 2858, 1695, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 1.21 (d, *J* = 6.1 Hz, 3 H), 1.29-1.42 (m, 1 H), 1.55-2.19 (m, 6 H), 2.58 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.13 (br s, 1 H), 3.49 (dd, *J* = 8.0, 1.8 Hz, 1 H), 4.07 (dq, *J* = 8.0, 6.1 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.60-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (s), 20.2 (q), 20.6 (q), 26.4 (t), 27.0 (q), 33.8 (t), 36.6 (d), 42.6 (t), 56.6 (d), 71.2 (d), 74.8 (d), 127.5 (d), 127.6 (d), 129.6 (d), 129.7 (d), 133.8 (s), 134.2 (s), 135.8 (d), 135.9 (d), 216.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_3Si$ 447.2331, found 447.2335.

Diastereoisomer **45.2b** had: FTIR (CH_2Cl_2 cast) 3462, 2957, 2931, 2858, 1702, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.2 Hz, 3 H), 1.08 (s, 9 H), 1.34-1.46 (m, 1 H), 1.68-2.08 (m, 4 H), 2.22-2.48 (m, 3 H), 2.74 (br s, 1 H), 3.67 (t, *J* = 5.0 Hz, 1 H), 4.09 (dq, *J* = 6.2, 5.0 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.60-7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.4 (s), 20.0 (q), 20.3 (q), 24.4 (t), 27.1 (q), 31.1 (t), 35.4 (d), 41.8 (t), 58.2 (d), 71.1 (d), 75.3 (d), 127.5 (d), 127.7 (d), 129.6 (d), 129.8 (d), 133.5 (s), 134.4 (s), 135.9 (d), 214.1 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_3Si$ 447.2331, found 447.2336.

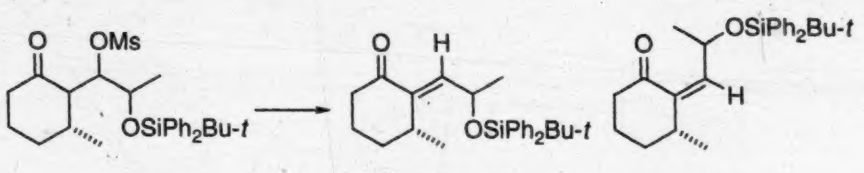
(*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]-3-methylcyclohexanone (45.3a,b). (a) Methanesulfonic Acid 2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-1-(6-methyl-2-oxocyclohexyl)propyl Ester.



45.2a,b --

$MeSO_2Cl$ (1.2 mL, 15 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **45.2a** and **45.2b** (2.0430 g, 4.8108 mmol) and Et_3N (3.4 mL, 24 mmol) in CH_2Cl_2 (80 mL). The cooling bath was left in place, but was not recharged. Stirring was continued for 4 h, the solution was quenched with saturated aqueous $NaHCO_3$ (18 mL), diluted with Et_2O (200 mL), washed with water and brine, dried ($MgSO_4$), and filtered through a pad (3 x 3 cm) of silica gel, using Et_2O (100 mL) as a rinse. Evaporation of the filtrate gave the crude mesylates (1.9542 g, ca 81%), which were used immediately for next step.

(b) (*E*)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]-3-methylcyclohexanone (45.3a,b).



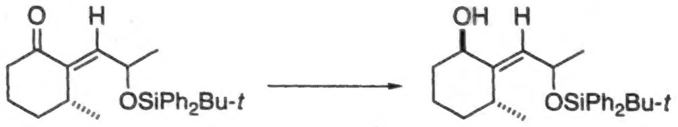
-- **45.3a** **45.3b**

DBU (1.8 mL, 12 mmol) was added dropwise to a stirred solution of the above mesylates (1.9542 g, 3.8870 mmol) in THF (40 mL). After 24 h, the mixture was diluted with Et_2O (200 mL), washed with water, 5% hydrochloric acid, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:10 EtOAc-hexane, gave enone **45.3** as two fractions, **45.3a** (more polar) (0.8343 g, 53%) and **45.3b** (less polar) (0.1450 g, 9%), each fraction consisting of two diastereoisomers (^1H NMR). Fraction **45.3a** [two diastereoisomers, ca 8:1 (^1H NMR)] had: FTIR (CH_2Cl_2 cast) 3071, 3049, 2960, 2931, 2891, 2857, 1691, 1629, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.61 (d, J = 7.2 Hz, 0.3 H), 0.81 (d, J = 7.3 Hz, 2.7 H), 1.02 (s, 8.0 H), 1.04 (s, 1.0 H), 1.20 (d, J = 6.4 Hz, 0.3 H), 1.25 (d. J = 6.3 Hz, 2.7 H), 1.20-2.80 (m, 7 H), 4.48-4.60 (m. 1 H), 6.32 (dd, J = 9.0, 1.0 Hz, 0.9 H), 6.45 (dd, J = 8.0, 0.7 Hz, 0.1 H), 7.30-7.50 (m, 6 H), 7.60-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.5 (t), 18.8 (t), 19.1 (s), 19.2 (q), 21.0 (q), 24.1 (q), 24.15 (q), 26.88 (q), 26.9 (q), 30.27 (d), 30.3 (t), 30.4 (t), 30.9 (d), 40.6 (t), 40.7 (t), 65.5 (d), 66.0 (d), 127.5 (d), 127.6 (d), 129.6 (d), 129.67 (d), 129.7 (d), 133.5 (s), 134.0 (s), 134.1 (s), 134.2 (s), 135.8 (d), 135.82 (d), 135.9

(d), 136.0 (d), 139.3 (s), 139.7 (d), 140.1 (d), 201.9 (s), 203.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{34}NaO_2Si$ 429.2226, found 429.2226. The *E* geometry for both components of this (major) fraction was inferred from the characteristic chemical shift (δ 6.45) of the vinyl hydrogen.

Fraction **45.3b** [two diastereoisomers, ca 5:1 (^{1}H NMR)] had: FTIR (CH_2Cl_2 cast) 3515, 2957, 2932, 2858, 1695, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90-1.90 (m, 20 H), 2.05-2.60 (m, 2 H), 4.65-4.85 (m, 1 H), 5.54-5.65 (m, 1 H), 7.25-7.42 (m, 6 H), 7.60-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.3 (q), 19.2 (t), 20.2 (t), 20.9 (q), 23.5 (s), 24.1 (q), 24.4 (q), 26.9 (q), 27.0 (q), 31.3 (t), 33.6 (t), 27.5 (d), 38.3 (d), 42.0 (t), 42.2 (t), 67.2 (d), 67.8 (d), 127.4 (d), 127.43 (d), 127.5 (d), 127.54 (d), 129.4 (d), 129.5 (d), 133.3 (s), 134.6 (s), 135.8 (d), 135.86 (d), 135.9 (d), 138.0 (d), 139,9 (s), 140.4 (s), 141.3 (d), 203.7 (s), 204.1 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{34}NaO_2Si$ 429.2226, found 429.2233. The *Z* geometry for both components of this (minor) fraction was inferred from the characteristic chemical shift (δ 5.54-5.65) of the vinyl hydrogen.

(1*R,*E*,3*R**)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]-3-methylcyclohexanol (45.4).**



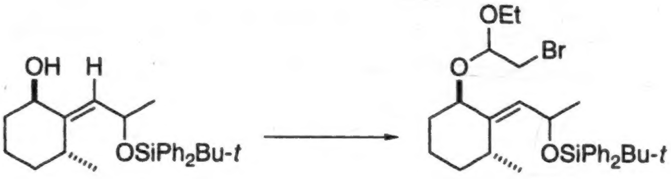
45.3a **45.4**

$NaBH_4$ (53.5 mg, 1.41 mmol) was added in small portions to a stirred and cooled (0 °C) solution of enones **45.3a** (two diastereoisomers, major fraction of **45.3**) (0.3790 g, 0.9320 mmol) and $CeCl_3.7H_2O$ (0.498 g, 1.34 mmol) in MeOH (10 mL). After 1 h, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with Et_2O (100 mL), and filtered through a pad (3 x 3 cm) of silica gel, using Et_2O (50 mL) as a rinse. The organic filtrate was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:8 EtOAc-hexane, gave alcohols **45.4** as a chromatographically inseparable mixture [ca 8:1 (^{1}H NMR)] of two diastereoisomers (0.3665 g, 96%): FTIR (CH_2Cl_2 cast) 3380, 3070, 3048, 2964, 2930, 2857 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72 (d, *J* = 7.3 Hz, 0.3 H), 0.89 (d, *J* = 7.4 Hz, 2.7 H), 0.92-1.70 (m, 6 H), 1.06 (s, 9 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.97-2.08 (m, 1 H), 2.50-2.68 (m, 1 H), 4.08 (t, *J* = 5.4 Hz, 1 H), 4.73 (dq, *J* = 8.3, 6.2 Hz, 1 H), 5.44 (dd, *J* = 7.9, 1.8 Hz, 0.1 H), 5.49 (dd, *J* = 8.3, 1.9 Hz, 0.9 H), 7.30-7.50 (m, 6 H), 7.62-7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.0 (q), 19.2 (s), 19.6 (t), 25.3 (q), 27.0 (q), 31.2 (d), 31.8 (t), 37.6 (t), 66.1 (d), 68.7 (d), 123.8 (d), 127.4 (d), 127.5 (d), 129.4 (d), 129.5 (d), 134.7

(s), 134.8 (s), 135.8 (d), 136.0 (d), 143.6 (s); the spectrum showed some peaks from minor diastereoisomer: δ 17.5 (q), 19.5 (t), 25.4 (q), 31.0 (d), 32.8 (t), 66.5 (d), 68.4 (d), 123.3 (d), 127.4 (d), 143.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_2Si$ 431.2382, found 431.2390.

As described in the discussion section, NOE measurements established that the OH and ring CH_3 groups are *trans* for both the major and minor diastereoisomers of **45.4**.

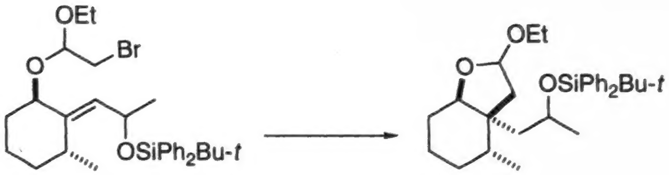
[[1-[(2*R**,*E*,6*R**)-2-(2-Bromo-1-ethoxyethoxy)-6-methylcyclohexylidene]-2-propyl]oxy](1,1-dimethylethyl)diphenylsilane (45.5).



45.4 **45.5**

NBS (0.4663 g, 2.620 mmol), dry CH_2Cl_2 (12 mL) and ethyl vinyl ether (0.84 mL, 8.8 mmol) was mixed under Argon until a clear solution was obtained. This solution was added dropwise by syringe to a stirred and cooled (0 °C) solution of alcohols **45.4** (0.3570 g, 0.8735 mmol) in CH_2Cl_2 (5 mL), the reaction mixture being protected from light by aluminum foil. The cold bath was left in place, and stirring was continued for 24 h. The mixture was then diluted with CH_2Cl_2 (100 mL), washed with 10% aqueous $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:20 EtOAc-hexane, gave bromoacetals **45.5** (0.315 g, 64%) as a mixture [ca 8:8:1:1 (^1H NMR)] of four diastereoisomers: FTIR (CH_2Cl_2 cast) 3070, 3048, 2965, 2930, 2889, 2858 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.50-0.78 (m, 3 H), 0.90-1.45 (m, 20 H), 1.78-1.98 (m, 1 H), 2.35-2.55 (m, 1 H), 3.05-3.56 (m, 4 H), 3.88-4.10 (m, 1 H), 4.55-4.88 (m, 2 H), 5.86-6.10 (m, 1 H), 7.18-7.32 (m, 6 H), 7.74-7.90 (m, 4 H); ^{13}C NMR (C_6D_6, 75.5 MHz) (signals for the two major diastereoisomers) δ 15.4 (q), 15.42 (q), 18.67 (q), 18.7 (q), 19.5 (s), 20.0 (t), 20.1 (t), 20.2 (t), 25.6 (q), 25.7 (q), 27.2 (q), 31.6 (d), 31.7 (d), 31.8 (d), 32.0 (t), 32.3 (t), 32.4 (t), 32.6 (t), 33.2 (t), 35.0 (t), 35.6 (t), 36.0 (t), 36.5 (t), 61.0 (t), 61.3 (t), 66.6 (d), 66.63 (d), 67.1 (d), 73.1 (d), 73.7 (d), 73.8 (d), 73.9 (d), 100.6 (d), 100.9 (d), 101.1 (d), 101.3 (d), 125.5 (d), 125.7 (d), 126.0 (d), 127.8 (d), 127.9 (d), 129.7 (d), 129.9 (d), 130.2 (d), 134.8 (s), 135.1 (s), 136.2 (d), 136.3 (d), 136.35 (d), 136.45 (d), 126.47 (d), 140.7 (s), 141.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{43}{}^{79}BrNaO_3Si$ 581.2063, found 581.2069.

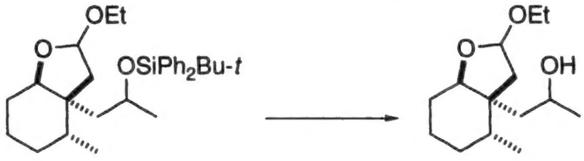
(3a*R,4*S**,7a*S**)-3a-[2-[[(1,1-(Dimethylethyl)-diphenylsilyl]oxy]propyl]-2-ethoxyoctahydro-4-methyl-benzofuran (45.6).**



45.5 **45.6**

Bu_3SnH (0.20 mL, 0.74 mmol) and AIBN (12.5 mg, 0.08 mmol) were added to a stirred solution of bromoacetals **45.5** (0.2702 g, 0.4828 mmol) in PhMe (35 mL). The flask was then lowered into a preheated oil bath set at 115 °C (continued stirring). After 1.5 h, the mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:25 EtOAc-hexane, gave acetals **45.6** (0.170 g, 73%) as a mixture of four diastereoisomers (^1H NMR): FTIR (CH_2Cl_2 cast) 3070, 3049, 2959, 2931, 2858 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.55-2.40 (m, 29 H), 3.25-3.55 (m, 1 H), 3.75-4.20 (m, 3 H), 4.95-5.06 (m, 1 H), 7.15-7.30 (m, 6 H), 7.70-7.90 (m, 4 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 13.7 (q), 15.6 (q), 15.8 (q), 16.0 (q), 16.4 (q), 17.0 (s), 19.39 (s), 19.41 (s), 20.4 (q), 20.9 (t), 21.0 (t), 25.4 (t), 25.5 (t), 25.6 (q), 25.9 (q), 26.4 (q), 26.5 (t), 27.0 (t), 27.2 (q), 27.3 (q), 28.6 (t), 29.8 (t), 29.9 (t), 34.5 (d), 34.7 (d), 36.0 (d), 36.7 (d), 37.1 (t), 37.7 (t), 37.8 (t), 37.9 (t), 41.8 (s), 42.3 (s), 43.0 (t), 43.26 (t), 43.34 (t), 45.2 (t), 45.6 (t), 63.2 (t), 63.4 (t), 64.0 (t), 67.9 (d), 68.2 (d), 68.3 (d), 76.4 (d), 77.5 (d), 79.9 (d), 80.3 (d), 102.4 (d), 102.8 (d), 103.3 (d), 127.8 (d), 128.3 (d), 129.8 (d), 129.85 (d), 129.9 (d), 130.0 (d), 130.1 (d), 134.3 (s), 134.5 (s), 134.56 (s), 134.6 (s), 135.16 (s), 135.2 (s), 136.2 (d), 136.3 (d); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{44}NaO_3Si$ 503.2957, found 503.2958.

1-[(3a*R,4*S**,7a*S**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanol (45.7a,b).**

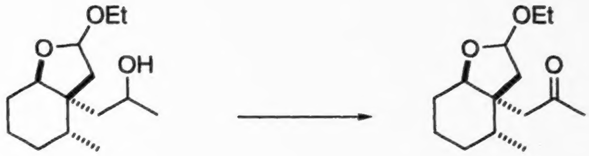


45.6 **45.7a,b**

Bu$_4$NF (1.0 M in THF, 1.0 mL, 1.0 mmol) was added dropwise to a stirred solution of acetals **45.6** (four diastereoisomers) (0.1615 g, 0.3359 mmol) in THF (15 mL). The stirred mixture was warmed to 45 °C for 4 h, cooled to room temperature, diluted with Et_2O (80 mL), and washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel (1 x 20 cm) using 1:4 EtOAc-hexane giving alcohol **45.7** as two fractions, **45.7a** (less polar) (36.0 mg, 44%) and **45.7b** (more polar) (34.5 mg, 42%), each fraction consisting of two diastereoisomers. Fraction **45.7a** [(two diastereoisomers, ca 6:1 (^{1}H NMR)] had: FTIR (CH_2Cl_2 cast) 3438, 2960, 2931 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.73 (d, J = 7.0 Hz, 3 H), 0.78 (s, 1 H), 0.95 (d, J = 6.2 Hz, 3 H), 1.06-1.23 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.29-1.62 (m, 4 H), 1.74-2.50 (m, 5 H), 3.48 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.74-3.87 (m, 1 H), 4.01 (dq, *J* = 9.5, 7.1 Hz, 1 H), 4.49 (t, *J* = 2.8 Hz, 1 H), 5.15 (dd, *J* = 5.8, 4.0 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) (signals for major diastereoisomer only) δ 15.6 (q), 16.2 (q), 21.1 (t), 25.5 (t), 26.3 (q), 30.0 (t), 36.2 (d), 36.6 (t), 43.0 (t), 45.9 (s), 63.4 (t), 64.5 (d), 77.7 (d), 102.5 (d); exact mass *m/z* calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1876.

Fraction **45.7b** [(two diastereoisomers, ca 6:1 (^{1}H NMR)] had: FTIR (CH_2Cl_2 cast) 3438, 2961, 2931, 2875 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 0.69 (br s, 1 H), 0.81 (d, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 6.2 Hz, 3 H), 0.94-1.50 (m, 9 H), 1.60-2.17 (m, 4 H), 2.26-2.56 (m, 1 H), 3.49 (dq, *J* = 9.6, 7.0 Hz, 1 H), 3.50-3.62 (m, 1 H), 4.01 (dq, *J* = 9.6, 7.0 Hz, 1 H), 4.14 (t, *J* = 3.5 Hz, 1 H), 5.18 (dd, *J* = 6.8, 2.2 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) (signals for major diastereoisomer only) δ 15.8 (q), 16.5 (q), 21.0 (t), 26.3 (q), 26.7 (t), 30.0 (t), 34.4 (d), 38.1 (t), 41.9 (t), 44.0 (s), 63.9 (t), 64.7 (d), 80.9 (d), 103.4 (d); exact mass *m/z* calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1879.

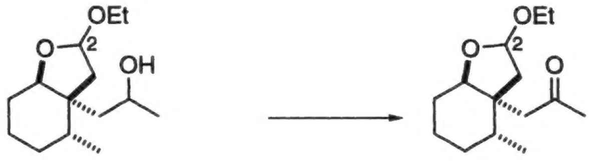
1-[(3a*R**,4*R**,7a*R**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanone (45.8) from 45.7a (major fraction of 45.7).



45.7a **45.8**

A solution of alcohols **45.7a** (two diastereoisomers, major fraction of **45.7**) (30.0 mg, 0.124 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred mixture of PCC (41 mg, 0.19 mmol), powdered 4 Å molecular sieves (180 mg) and CH_2Cl_2 (1.2 mL). After 2 h, the mixture was diluted with Et_2O (10 mL), and filtered through a pad (2 x 1.5 cm) of silica gel, using Et_2O (50 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:2 EtOAc-hexane, gave ketone **45.8** as a single diastereoisomer (24 mg, 81%): FTIR (CH_2Cl_2 cast) 2932, 1719 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.69 (d, J = 7.0 Hz, 3 H), 0.89 (dq, J = 13.2, 3.2 Hz, 1 H), 1.19-1.51 (m, 4 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.68-1.80 (m, 1 H), 1.73 (s, 3 H), 1.83 (d, J = 15.5 Hz, 1 H), 1.98-2.07 (m, 1 H), 2.17 (d, J = 15.5 Hz, 1 H), 2.23 (dd, J = 13.9, 4.4 Hz, 1 H), 2.38 (dd, J = 13.9, 6.0 Hz, 1 H), 3.43 (dq, J = 9.4, 7.1 Hz, 1 H), 3.94 (dq, J = 9.4, 7.1 Hz, 1 H), 4.02 (t, J = 2.8 Hz, 1 H), 5.10 (dd, J = 5.9, 4.5 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.5 (q), 17.1 (q), 20.7 (t), 25.5 (t), 30.0 (t), 31.6 (q), 35.7 (d), 41.8 (t), 43.1 (t), 46.0 (s), 63.6 (t), 79.0 (d), 102.9 (d), 205.7 (s); exact mass m/z calcd for $C_{14}H_{24}O_3$ 240.1726, found 240.1728.

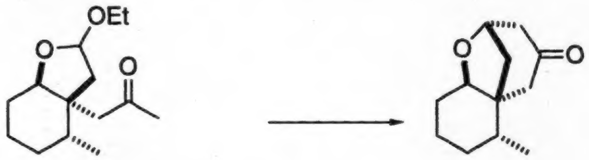
1-[(3a*R**,4*R**,7a*R**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanone (45.8′) from 45.7b (minor fraction of 45.7).



45.7b **45.8′**

A solution of alcohols **45.7b** (two diastereoisomers, minor fraction of **45.7**) (10.0 mg, 0.0413 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred mixture of PCC (14 mg, 0.065 mmol), powdered 4 Å molecular sieves (60 mg) and CH_2Cl_2 (0.5 mL). After 5 h, the mixture was diluted with Et_2O (10 mL), and filtered through a pad (2 x 1.5 cm) of silica gel, using Et_2O (20 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 15 cm), using 1:5 EtOAc-hexane, gave ketone **45.8′** as a single diastereoisomer (8.6 mg, 87%). Compounds **45.8** and **45.8′** have different stereochemistry at C(2). Compound **45.8′** had: FTIR (CH_2Cl_2 cast) 2932, 2874, 1716 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.73 (d, *J* = 7.0 Hz, 3 H), 0.87-1.01 (m, 1 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.32-1.44 (m, 3 H), 1.70 (s, 3 H), 1.76-1.92 (m, 1 H), 1.91 (d, *J* = 16.0 Hz, 1 H), 2.01-2.11 (m, 1 H), 2.15 (d, *J* = 16.0 Hz, 1 H), 2.21 (d, *J* = 1.9 Hz, 1 H), 2.35-2.46 (m, 1 H), 2.49 (dd, *J* = 13.6, 7.1 Hz, 1 H), 3.42 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.91 (t, *J* = 3.4 Hz, 1 H), 3.94 (dq, *J* = 9.6, 7.1 Hz, 1 H), 5.13 (dd, *J* = 7.1, 1.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.7 (q), 17.0 (q), 20.7 (t), 26.8 (t), 30.0 (t), 31.8 (q), 34.2 (d), 41.5 (t), 41.9 (t), 44.3 (s), 64.1 (t), 80.5 (d), 103.6 (d), 206.3 (s); exact mass *m/z* calcd for $C_{14}H_{24}O_3$ 240.1726, found 240.1723.

(1*R,2*R**,6*R**,8*S**)-2-Methyl 7-oxatricyclo-[6.3.1.0^{1,6}]dodecan-10-one (45.9).**

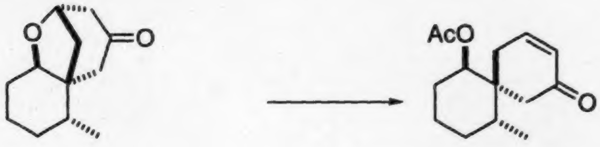


45.8 & 45.8′ **45.9**

A solution of ketones **45.8** and **45.8′** (ca 2:1) (16.0 mg, 0.067 mmol) in a mixture of 3 M hydrochloric acid (3.3 mL) and THF (0.68 mL) was refluxed (85 °C) for 36 h, cooled to room temperature, and extracted with EtOAc (20 mL). The aqueous layer was washed with EtOAc (2 x 10 mL), and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 20 cm), using EtOAc-hexane, gave tricyclic ketone **45.9** (10 mg, 77%): FTIR (CH_2Cl_2 cast) 2939, 2867, 1716 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.96 (d, *J* = 7.2 Hz, 3 H), 1.20-1.82 (m, 7 H), 1.92-2.04 (m, 1 H), 2.22 (d, *J* = 17.5 Hz, 1 H), 2.28 (d, *J* = 17.5 Hz, 1 H), 2.40-2.58 (m, 3 H), 3.75 (dd, *J* = 11.0, 6.0 Hz, 1 H), 4.47 (ddd, *J* =

6.4, 3.7, 1.6 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 16.7 (q), 18.4 (t), 28.1 (t), 30.4 (t), 34.1 (d), 39.0 (t), 45.9 (s), 49.6 (t), 52.1 (t), 73.6 (d), 87.7 (d), 210.4 (s); exact mass *m/z* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1312.

Acetic Acid (1*R,5*R**,6*R**)-5-Methyl-10-oxospiro-[5.5]undec-8-en-1-yl Ester (45.10).**

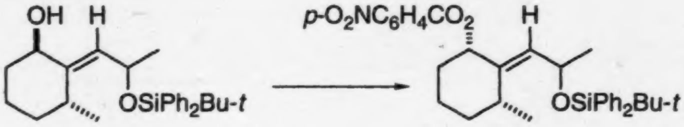


45.9 **45.10**

A solution of ketone **45.9** (4.8 mg, 0.025 mmol), TsOH.H_2O (4.0 mg, 0.02 mmol), and Ac_2O (0.04 mL, 0.4 mmol) in PhH (4.5 mL) was heated at 85 °C for 28 h, cooled, and evaporated. The residue was diluted with Et_2O (30 mL), washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 25 cm), using 2:5 EtOAc-hexane, gave spiro enone **45.10** (3.6 mg, 62%): FTIR (CH_2Cl_2 cast) 2938, 2868, 1734, 1680 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.66 (d, *J* = 7.2 Hz, 3 H), 0.87-1.02 (m, 1 H), 1.12-1.58 (m, 5 H), 1.62-1.74 (m, 1 H), 1.69 (s, 3 H), 1.88-2.05 (m, 2 H), 2.27 (d, *J* = 16.0 Hz, 1 H), 2.29 (d, *J* = 16.0 Hz, 1 H), 5.06 (dd, *J* = 6.5, 3.5 Hz, 1 H), 6.02 (dt, *J* = 10.1, 2.1 Hz, 1 H), 6.19 (dt, *J* = 10.1, 4.2 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.7 (q), 19.5 (t), 20.3

(q), 25.8 (t), 28.5 (t), 31.1 (t), 33.8 (d), 42.1 (s or t), 42.8 (s or t), 72.9 (d), 129.2 (d), 146.3 (d), 168.8 (s), 196.6 (s); exact mass *m/z* calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1415.

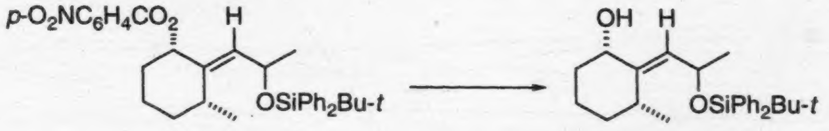
(1*R,*E*,3*S**)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]-3-methylcyclohexanol (46.1a,b). (a) 4-Nitrobenzoic Acid (1*R**,*E*,3*S**)-2-[2-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]propylidene]-3-methylcyclohexyl Ester.**



45.4 --

Ph$_3$P (0.802 g, 3.06 mmol) and 4-nitrobenzoic acid (0.5117 g, 3.06 mmol) were added successively to a stirred and cooled (0 °C) solution of allylic alcohols **45.4** (8:1 mixture of diastereoisomers) (0.6253 g, 1.530 mmol) in dry THF (15 mL). DEAD (0.48 mL, 3.05 mmol) was added dropwise, and stirring was continued for 90 min at 0 °C. The mixture was then diluted with Et$_2$O (150 mL), washed successively with saturated aqueous NaHCO$_3$, water and brine, dried (MgSO$_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:15 EtOAc-hexane, gave the crude nitrobenzoates (0.785 g), which were used directly in next step.

(b) (1*R**,*E*,3*S**)-2-[2-[[(1,1-(Dimethylethyl)-diphenylsilyl]oxy]propylidene]-3-methylcyclohexanol (46.1a,b).



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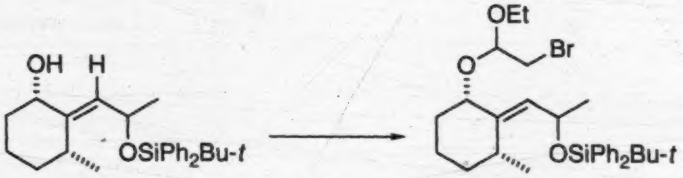
46.1a,b

KOH (0.79 g, 14 mmol) was added to a stirred solution of the above crude nitrobenzoates (ca 0.785 g, ca 1.407 mmol) in MeOH (50 mL), and stirring was continued for 4 h. The solvent was evaporated and the residue was diluted with water (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 40 cm), using 1:8 EtOAc-hexane, gave alcohols **46.1** as two separable diastereoisomers, **46.1a** (more polar) (0.299 g, 48%) and **46.1b** (less polar) (0.0765 g, 12%). Diastereoisomer **46.1a** had: FTIR (CH_2Cl_2 cast) 3387, 3070, 3048, 2931, 2857, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.48 (m, 8 H), 1.06 (s, 9 H), 1.23 (d, *J* = 6.2, 3 H), 1.78-1.98 (m, 2 H), 2.26-2.38 (m, 1 H), 4.12 (t, *J* = 2.5 Hz, 1 H), 4.64 (dq, *J* = 8.3, 6.2 Hz, 1 H), 5.45 (d, *J* = 8.3 Hz, 1 H), 7.28-7.48 (m, 6 H), 7.60-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.0 (t), 19.1 (s), 21.4 (q), 25.0 (q), 26.9 (q), 29.9 (d), 31.9 (t), 33.5 (t), 65.3 (d), 74.9 (d), 127.4 (d), 127.5 (d), 129.4 (d), 129.5 (d), 133.0 (d), 134.4 (s), 134.5 (s), 135.8 (d), 135.9 (d), 141.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_2Si$ 431.2382, found 431.2375.

Diastereoisomer **46.1b** had: FTIR (CH_2Cl_2 cast) 3578, 3463, 3070, 3049, 2931, 2857, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72 (s, 1 H), 0.78 (d, *J* = 7.3, 3 H), 1.07 (s, 9 H), 1.18-1.52 (m, 4 H), 1.22 (d, *J* = 7.2 Hz, 3 H), 1.74-1.95 (m, 2 H), 2.32-2.45 (m, 1 H), 3.98 (t, *J* = 2 Hz, 1 H), 4.65 (dq, *J* = 7.8, 6.3 Hz, 1 H), 5.32 (d, *J* = 7.8 Hz, 1 H), 7.30-7.52 (m, 6 H), 7.60-7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.0 (t), 19.2 (s), 19.9 (q), 24.9 (q), 27.0 (q), 29.4 (d), 32.7 (t), 33.3 (t), 66.1 (d), 74.4 (d), 127.4 (d), 127.6 (d), 129.6 (d), 132.9 (d), 134.3 (s), 134.8 (s), 135.9 (d), 136.1 (d), 136.3 (d), 141.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_2Si$ 431.2382, found 431.2374.

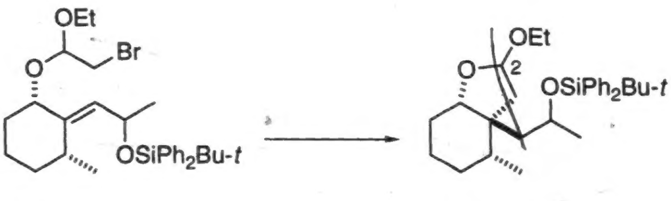
[[1-[(2*R**,*E*,6*S**)-2-(2-Bromo-1-ethoxyethoxy)-6-methylcyclohexylidene]-2-propyl]oxy](1,1-dimethylethyl)diphenylsilane (46.2).



46.1a **46.2**

NBS (0.353 g, 1.98 mmol), dry CH_2Cl_2 (9 mL) and ethyl vinyl ether (0.64 mL, 6.6 mmol) were mixed under Ar in a 50-mL round-bottomed flask until a homogeneous solution was obtained. This solution was added dropwise by syringe to a stirred and cooled (0 °C) solution of alcohol **46.1a** (i.e. major diastereoisomer) (0.2702 g, 0.6612 mmol) in CH_2Cl_2 (4 mL), the reaction mixture being protected from light by aluminum foil. The cold bath was left in place, and stirring was continued for 26 h. The mixture was then diluted with CH_2Cl_2 (80 mL), washed with 10% aqueous $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 40 cm), using 1:20 EtOAc-hexane, gave bromoacetals **46.2** as a chromatographically inseparable mixture [ca 1:1 (^{1}H NMR)] of diastereoisomers (0.2319 g, 63%): FTIR (CH_2Cl_2 cast) 3070, 3048, 2964, 2931, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.66-1.46 (m, 22 H), 1.83-2.06 (m, 2 H), 2.28-2.42 (m, 1 H), 3.05-3.4 (m, 4 H), 3.84 (t, *J* = 1.5 Hz, 0.5 H), 4.05 (t, *J* = 2 Hz, 0.5 H), 4.58 (t, *J* = 5.4 Hz, 0.5 H), 4.72 (dd, *J* = 6.0, 4.7 Hz, 0.5 H), 4.74-4.88 (m, 1 H), 5.54 (d, *J* = 8.3 Hz, 0.5 H), 5.60 (d, *J* = 8.3 Hz, 0.5 H), 7.16-7.28 (m, 6 H), 7.72-7.88 (m, 4 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.2 (q), 15.4 (q), 15.8 (t), 15.9 (t), 19.4 (s), 20.6 (q), 20.7 (q), 25.2 (q), 25.5 (q), 27.16 (q), 27.2 (q), 30.3 (d), 30.6 (d), 32.2 (t), 32.3 (t), 32.5 (t), 32.9 (t), 33.4 (t), 60.6 (t), 61.3 (t), 65.9 (d), 78.3 (d), 80.0 (d), 98.8 (d), 100.9 (d), 127.8 (d), 127.9 (d), 129.8 (d), 130.0 (d), 133.4 (d), 134.7 (s), 134.76 (s), 134.8 (s), 135.4 (d), 136.1 (d), 136.2 (d), 137.8 (s), 139.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{43}{}^{79}BrNaO_3Si$ 581.2063, found 581.2057.

(3a*R**,4*R**,7a*S**)-3a-[2-[[(1,1-(Dimethylethyl)-diphenylsilyl]oxy]propyl]-2-ethoxyoctahydro-4-methyl-benzofuran (46.3a,b).

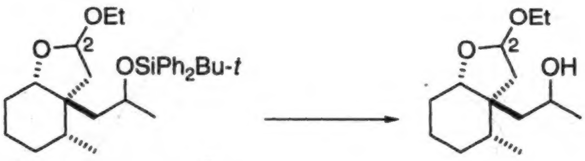


46.2 **46.3a,b**

Bu_3SnH (0.15 mL, 0.56 mmol) and AIBN (9.0 mg, 0.055 mmol) were added to a stirred solution of bromoacetals **46.2** (0.1940 g, 0.3466 mmol) in PhMe (25 mL). The flask was then lowered into a preheated oil bath set at 115 °C (continued stirring). After 1 h, the mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:40 EtOAc-hexane gave acetals **46.3** as two separable diastereoisomers, **46.3a** (more polar) (82 mg, 49%) and **46.3b** (less polar) (40 mg, 24%), differing in stereochemistry at C(2). Diastereoisomer **46.3a** had: FTIR (CH_2Cl_2 cast) 3070, 3048, 2931, 2857 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.82 (d, *J* = 7.0 Hz, 3 H), 0.87-1.73 (m, 24 H), 2.07 (dd, *J* = 13.5, 6.2 Hz, 1 H), 2.34 (dd, *J* = 14.5, 5.0 Hz, 1 H), 3.42 (dq, *J* = 9.4, 7.1 Hz, 1 H), 3.96 (dq, *J* = 9.4, 7.1 Hz, 1 H), 4.02-4.13 (m, 2 H), 5.09 (dd, *J* = 6.1, 2.6 Hz, 1 H), 7.16-7.28 (m, 6 H), 7.75-7.90 (m, 4 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.3 (q), 16.9 (q), 17.2 (t), 19.1 (s), 25.5 (q), 26.7 (t), 27.0 (q), 28.1 (t), 31.3 (d), 42.0 (t), 45.6 (t), 46.7 (s), 63.0 (t), 68.3 (d), 80.6 (d), 103.2 (d), 127.5 (d), 128.0 (d), 129.5 (d), 129.6 (d), 134.5 (s), 135.2 (s), 136.1 (s); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{44}NaO_3Si$ 503.2957, found 503.2957.

Diastereoisomer **46.3b** had: FTIR (CH_2Cl_2 cast) 3070, 3048, 2965, 2931, 2857 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.68 (d, *J* = 6.7 Hz, 3 H), 0.85-1.75 (m, 22 H), 1.84-2.07 (m, 2 H), 2.05 (dd, *J* = 13.4, 5.4 Hz, 1 H), 2.23 (dd, *J* = 14.6, 5.4 Hz, 1 H), 3.44 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.97 (dq, *J* = 9.5, 7.0 Hz, 1 H), 4.12-4.23 (m, 2 H), 5.18 (t, *J* = 5.7 Hz, 1 H), 7.16-7.30 (m, 6 H), 7.75-7.92 (m, 4 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.7 (q), 17.4 (q), 19.4 (s), 23.3 (t), 26.4 (q), 27.31 (q), 30.6 (t), 31.5 (t), 34.5 (d), 39.3 (t), 47.7 (s or t), 49.2 (s or t), 63.7 (t), 68.3 (d), 80.2 (d), 104.6 (d), 127.8 (d), 128.3 (d), 129.8 (d), 129.9 (d), 134.7 (s), 135.6 (s), 136.4 (d); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{44}NaO_3Si$ 503.2952, found 503.2954.

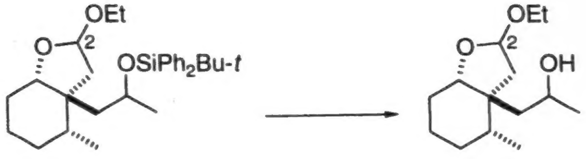
1-[(3a*R**,4*R**,7a*S**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanol (46.4) from 46.3a (major diastereoisomer of 46.3).



46.3a **46.4**

Bu_4NF (1.0 M in THF, 0.5 mL, 0.5 mmol) was added dropwise to a stirred solution of acetals **46.3a** (i.e. major diastereoisomer) (80 mg, 0.17 mmol) in THF (7 mL). The stirred mixture was warmed to 45 °C for 6 h, cooled to room temperature, diluted with Et_2O (50 mL), and washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 30 cm), using 1:4 EtOAc-hexane, gave alcohol **46.4** (32 mg, 80%): FTIR (CH_2Cl_2 cast) 3439, 2960, 2930 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.77 (d, J = 6.8 Hz, 3 H), 1.05-1.75 (m, 8 H), 1.15 (t, J = 7.1 Hz, 3 H), 1.18 (d, J = 6.1 Hz, 3 H), 1.89 (dd, J = 13.8, 1.6 Hz, 1 H), 1.98 (dd, J = 13.8, 6.0 Hz, 1 H), 2.08 (dd, J = 14.7, 9.7 Hz, 1 H), 2.81 (br s, 1 H), 3.34 (dq, J = 9.5, 7.1 Hz, 1 H), 3.84 (dq, J = 9.5, 7.1 Hz, 1 H), 4.01-4.13 (m, 1 H), 4.29 (dd, J = 5.4, 4.1 Hz, 1 H), 5.04 (dd, J = 6.0, 1.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.3 (q), 16.9 (q), 18.3 (t), 25.7 (q), 26.1 (t), 27.4 (t), 34.6 (d), 38.7 (t), 45.5 (s or t), 47.8 (s or t), 63.0 (t), 64.5 (d), 80.7 (d), 103.3 (d); exact mass m/z calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1883.

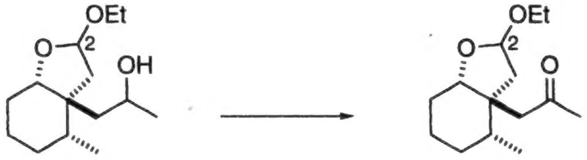
1-[(3a*R,4*R**,7a*S**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanol (46.4′) from 46.3b (minor diastereoisomer of 46.3).**



46.3b **46.4′**

Bu_4NF (1.0 M in THF, 0.25 mL, 0.25 mmol) was added dropwise to stirred a stirred solution of acetals **46.3b** (i.e. minor diastereoisomer) (38 mg, 0.08 mmol) in THF (4 mL). The stirred mixture was warmed to 45 °C for 6 h, cooled to room temperature, diluted with Et_2O (40 mL), and washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 30 cm), using 1:4 EtOAc-hexane, gave alcohol **46.4′** (14.5 mg, 76%). Compounds **46.4** and **46.4′** have different stereochemistry at C(2). Compound **46.4′** had: FTIR (CH_2Cl_2 cast) 3417, 2960, 2930, 2874 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.73 (d, J = 6.8 Hz, 3 H), 0.96-1.18 (m, 3 H), 1.02 (d, J = 6.2 Hz, 3 H), 1.21-1.36 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.48-1.61 (m, 2 H), 1.65 (dd, J = 13.3, 6.1 Hz, 1 H), 1.70 (dd, J = 14.9, 9.2 Hz, 1 H), 1.86-2.10 (m, 2 H), 2.11 (dd, J = 13.2, 5.4 Hz, 1 H), 3.47 (dq, J = 9.5, 7.1 Hz, 1 H), 3.80-3.90 (m, 1 H), 4.00 (dq, J = 9.5, 7.1 Hz, 1 H), 4.35 (dd, J = 10.8, 6.6 Hz, 1 H), 5.29 (t, J = 5.7 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.7 (q), 17.5 (q), 23.4 (t), 26.2 (q), 30.7 (t), 31.5 (t), 34.6 (d), 39.3 (t), 46.7 (s or t), 49.0 (s or t), 63.8 (t), 64.9 (d), 80.9 (d), 104.9 (d); exact mass m/z calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1880.

1-[(3a*R**,4*R**,7a*S**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanone (46.5) from 46.4 (major diastereoisomer series).

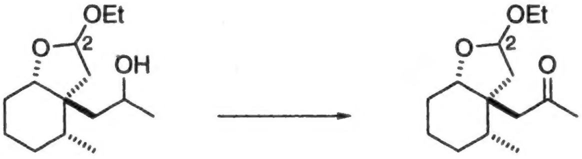


46.4 **46.5**

A solution of alcohol **46.4** (major diastereoisomer series) (26 mg, 0.11 mmol) in CH_2Cl_2 (2.6 mL) was added dropwise to a stirred mixture of PCC (36 mg, 0.17 mmol), powdered 4 Å molecular sieves (156 mg) and CH_2Cl_2 (1 mL). After 3 h, the mixture was diluted with Et_2O (10 mL), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (50 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 25 cm), using 1:2 EtOAc-hexane, gave ketone **46.5** (20.8 mg, 81%): FTIR (CH_2Cl_2 cast) 2931, 2872, 1715 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.77 (d, *J* = 6.9 Hz, 3 H), 0.98-1.08 (m, 1 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 1.26-1.39 (m, 2 H), 1.44-1.65 (m, 2 H), 1.46 (dd, *J* = 13.5, 1.4 Hz, 1 H), 1.69 (s, 3 H), 1.88-1.99 (m, 1 H), 2.10-2.20 (m, 1 H), 2.12 (dd, *J* = 13.5, 6.2 Hz, 1 H), 2.37 (d, *J* = 17.5 Hz, 1 H), 3.05 (d, *J* = 17.5 Hz, 1 H), 3.38 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.89 (dq, *J* = 9.5, 7.1 Hz, 1 H), 4.52 (dd, *J* = 6.9, 5.0 Hz, 1 H), 5.07 (dd, *J* = 6.2, 1.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.6 (q), 17.3 (q), 19.1

(t), 28.6 (t), 29.0 (t), 31.3 (d or q), 31.6 (d or q), 39.6 (t), 45.9 (s or t), 49.5 (s or t), 63.3 (t), 81.4 (d), 103.0 (d), 206.6 (s); exact mass *m/z* calcd for $C_{14}H_{24}O_3$ 240.1726, found 240.1723.

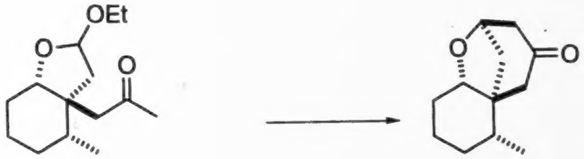
1-[(3a*R**,4*R**,7a*S**)-2-Ethoxyoctahydro-4-methylbenzofuran-3a-yl]-2-propanone (46.5′) from 46.4′ (minor diastereoisomer series).



46.4′ **46.5′**

A solution of alcohol **46.4′** (minor diastereoisomer series) (13 mg, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a stirred mixture of PCC (18 mg, 0.08 mmol), powdered 4 Å molecular sieves (80 mg) and CH_2Cl_2 (0.5 mL). After 3 h, the mixture was diluted with Et_2O (5 mL), and filtered through a pad (2 x 2 cm) of silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 30 cm), using 1:2 EtOAc-hexane, gave ketone **46.5′** (10 mg, 78%). Compounds **46.5** and **46.5′** have different stereochemistry at C(2). Compound **46.5′** had: FTIR (CH_2Cl_2 cast) 2931, 1716 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.70 (d, *J* = 6.8 Hz, 3 H), 0.90-1.33 (m, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.50 (d of quintets, J = 13.1, 3.4 Hz, 1 H), 1.69-2.05 (m, 3 H), 1.75 (dd, J = 13.5, 6.1 Hz, 1 H), 1.81 (s, 3 H), 2.03 (dd, J = 13.5, 5.2 Hz, 1 H), 2.06 (d, J = 15.1 Hz, 1 H), 2.30 (d, J = 15.1 Hz, 1 H), 3.42 (dq, J = 9.5, 7.1 Hz, 1 H), 3.93 (dq, J = 9.5, 7.1 Hz, 1 H), 4.26 (dd, J = 10.7, 6.7 Hz, 1 H), 5.14 (dd, J = 6.1, 5.2, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 15.6 (q), 17.7 (q), 23.1 (t), 30.6 (t), 31.3 (t), 32.0 (q), 35.0 (d), 37.8 (t), 49.5 (t), 50.7 (s), 63.8 (t), 81.1 (d), 104.6 (d), 206.8 (s); exact mass m/z calcd for $C_{14}H_{24}O_3$ 240.1726, found 240.1727.

(1*R,2*S**,6*R**,8*S**)-2-Methyl-7-oxatricyclo-[6.3.1.0^{1,6}]dodecan-10-one (46.6).**

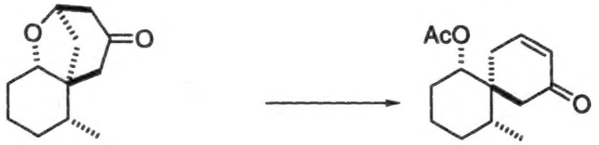


46.5 & **46.5′** **46.6**

A solution of ketones **46.5** and **46.5′** (ca 2:1 mixture of diastereoisomers) (17.5 mg, 0.073 mmol) in a mixture of 3 M hydrochloric acid (3.6 mL) and THF (0.75 mL) was refluxed (85 °C) for 6 h, cooled to room temperature, and extracted with EtOAc (30 mL). The aqueous layer was washed with EtOAc (2 x 10 mL), and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 30 cm),

using 1:3 EtOAc-hexane, gave tricyclic ketone **46.6** (12 mg, 85%): FTIR (CH_2Cl_2 cast) 2933, 2859, 1718 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 0.65 (d, J = 6.7 Hz, 3 H), 0.70-1.40 (m, 7 H), 1.74-1.84 (m, 3 H), 2.02 (dt, J = 16.9, 2.6 Hz, 1 H), 2.27 (d, J = 16.9 Hz, 1 H), 2.66 (ddt, J = 16.4, 4.0, 2.0 Hz, 1 H), 3.54 (d, J = 10.5, 6.4 Hz, 1 H), 4.20 (ddd, J = 6.7, 4.3, 1.1 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 17.6 (q), 22.7 (t), 30.8 (t), 32.5 (t), 32.7 (t), 36.7 (d), 47.0 (s), 49.5 (t), 54.2 (t), 73.5 (d), 83.5 (d), 207.7 (s); exact mass *m/z* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1307.

Acetic Acid (1*R**,5*S**,6*S**)-5-Methyl-10-oxospiro-[5.5]undec-8-en-1-yl Ester (46.7).



46.6 **46.7**

A solution of ketone **46.6** (11 mg, 0.06 mmol), $TsOH.H_2O$ (10 mg, 0.057 mmol), and Ac_2O (0.08 mL, 0.9 mmol) in PhH (12 mL) was heated at 85 °C for 23 h, cooled, and evaporated. The residue was diluted with Et_2O (50 mL), washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.6 x 30 cm), using 1:6 EtOAc-hexane, gave spiro enone **46.7** (4.5 mg, 34% or 49% after correction for recovered starting material): FTIR (CH_2Cl_2 cast) 3034, 2938, 2863,

1739, 1678 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 0.50 (d, *J* = 6.7 Hz, 3 H), 0.65-1.22 (m, 5 H), 1.27 (dt, *J* = 13.7, 3.8 Hz, 1 H), 1.56-1.73 (m, 2 H), 1.58 (s, 3 H), 2.00 (ddd, *J* = 20, 3.6, 2.6 Hz, 1 H), 2.16 (d, *J* = 16.3 Hz, 1 H), 2.29 (d, *J* = 16.3 Hz, 1 H), 4.46 (dd, *J* = 10.7, 4.1 Hz, 1 H), 5.94 (dt, *J* = 10.2, 2.3 Hz, 1 H), 6.13 (dt, *J* = 10.2, 4.1 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 17.5 (q), 20.5 (q), 22.8 (t), 25.1 (t), 26.7 (t), 29.1 (t), 40.7 (d), 43.2 (s), 46.6 (t), 79.3 (d), 129.5 (d), 146.7 (d), 169.3 (s), 197.4 (s); exact mass *m/z* calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1414.

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60 Phosphomolybdic acid (15 g) and $(NH_4)_2Ce(NO_3)_6$ (2.5 g) dissolved in a mixture of water (485 mL) and concentrated H_2SO_4 (15 mL).

61 *p*-Anisaldehyde (15 drops) was added to concentrated H_2SO_4 (6 mL) and EtOH (94 mL).

CHAPTER 2

The Total Synthesis of Cladobotryal and 2-*epi*-CJ-16,170

1 INTRODUCTION

1.1 General

Worldwide sales of antifungal agents for crop protection are at least US$ 6 billion.[1] Crompton Co., the supporting industrial partner for this project, has an important share[2] in the worldwide sales of agrochemicals, including antifungal agents. There is a growing need[3] for new antifungal agents in order to (a) combat the emergence of fungicide resistance, (b) provide more cost-effective crop treatments, and (c) increase the safety levels for manufacturers, users and consumers of the treated crops.

Cladobotryal (**1**), which is a metabolite of the fungus *Caldobotrium varium* Nees:Fries (CBS 331.95), was first described[4] in 1998. It was reported that cladobotryal exhibits a marked effect against the phytopathogenic fungi *Phytophthora cryptogea* and *Pythium ultimum* (Oomyceta), whereas the growth of ascomycetes, various imperfect fungi, yeast species, and bacteria was virtually unaffected. Consequently, **1** may be useful as an agricultural fungicide.[5] On this basis, compound **1** is of interest as a lead in the design of antifungal agents. A more recent publication[6] disclosed another potentially important biological property, as the compound was reported to show moderate antibacterial activity against some drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*. The related dihydrofuro[2,3-*b*]pyridinones CJ-16,169 (**2**), CJ-16,174 (**3**) and CJ-16,173 (**4**) (Figure 1), as well as cladobotryal **1** (also named CJ-15,696), were isolated[6] from the same organism (*C. varium*, CL 12284), but the parent heterocyclic system is a rare structural type and examination of the Beilstein database shows no other dihydrofuro[2,3-*b*]pyridinones besides those that are benzo-fused.[7] The compounds CJ-16,170 (**5**), CJ-16,171 (**6**), CJ-16,196 (**7**), CJ-16,170 (**8**) (Figure 1) with the isomeric and better-known[8] dihydrofuro[3,2-*c*]pyridinone structure were also isolated[6] from *C. varium* (CL 12284). Compound **5**, which is called CJ-16,170, is a reduced structural isomer of cladobotryal (Figure 1).

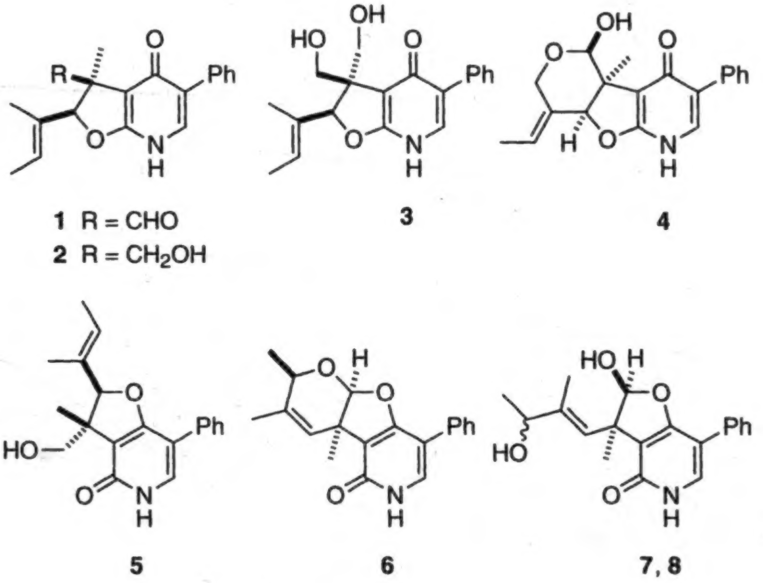
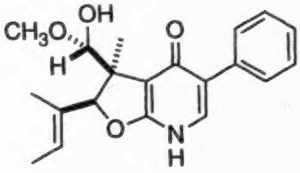


Figure 1 Structures of **1**-**8**

The structure of cladobotryal was assigned on the basis of NMR spectroscopic measurements (^1H, ^{13}C, HMQC and HMBC) and

X-Ray analysis of a crystalline derivative, the methanol hemiacetal **9**[4,6] (Figure 2). The absolute configurations of these furopyridinones have not yet been established. The optical rotation has been reported, however. The value for cladobotryal **1** is + 65° (*c* = 0.8, $CHCl_3$), and the value for hemiacetal **9** is + 46 ° (*c* = 0.7, MeOH).


CH3O
OH
H
O
O
N
H

9

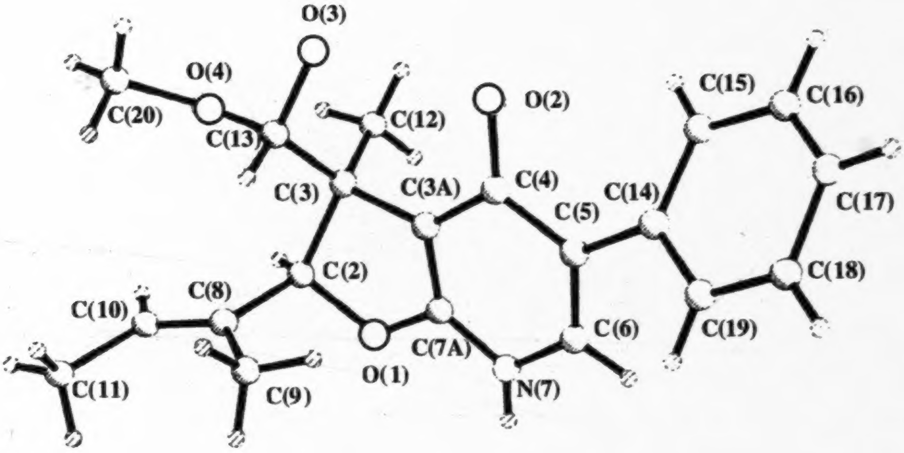
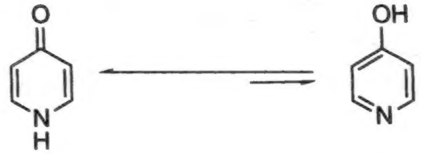

O(3)
O(4)
C(20)
C(13)
C(12)
O(2)
C(15)
C(16)
C(17)
C(3)
C(3A)
C(4)
C(5)
C(14)
C(2)
C(8)
C(10)
C(11)
C(9)
O(1)
C(7A)
N(7)
C(6)
C(19)
C(18)

Figure 2 Structure and crystal structure of cladobotryal methyl hemiacetal (**9**)

Cladobotryal was first assigned the pyridinone structure **1** (Figure 1),[4] but the more recent publication[6] assigns hydroxy-pyridine structures to compounds **1-8**. It is now well established that 2- and 4-pyridinones and their benzo-analogs exist predominantly in the oxo form, e.g. (**10a**) rather than the hydroxypyridine form, e.g. (**10b**)[9] (Figure 3). The enaminone system NH-C=C-C=O is considerably more stable than

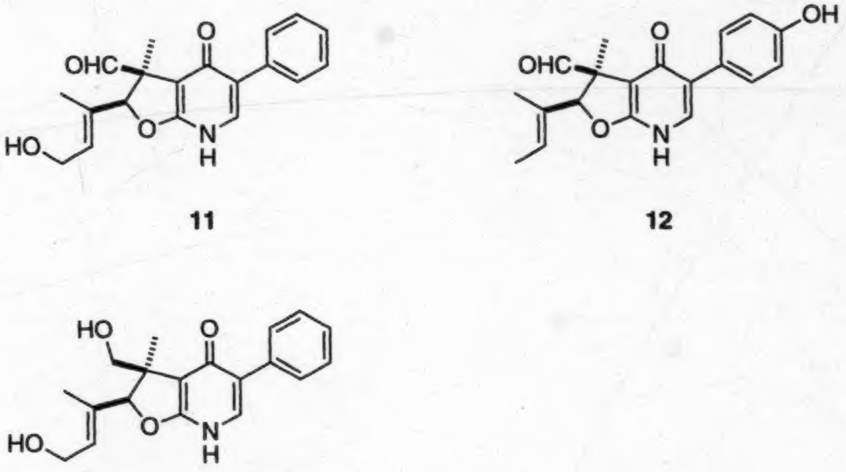

10a

10b

Figure 3 Structures of **10a** and **10b**

the alternative iminoenol system N=C-C=C-OH by a factor[9a,10] of ca 10^8 (oxo:enol = ca 10^8). On this basis, and for simplicity, the pyridinone tautomers will be used here.

Biotransformation of cladobotryal (**1**) was performed[6] in an attempt to improve antibiotic activity. One day after inoculation, test tube cultures of 92 microorganisms were fed with cladobotryal at a final concentration of 0.1 mg/mL. The fermentation broths were analyzed by HPLC 1 to 6 days after substrate addition, and it was found that *Calonectria decora*, *Cunninghamella echinulata var. elegans*, and *Actinomyces sp.* produced new pyridinone derivatives that were later isolated from larger scale fermentations and assigned as CP-741,326 (**11**), CP-473,195 (**12**) and CP-473,198 (**13**). The structures of these biotransformation products were readily deduced, as shown in Figure 4, by comparisons of molecular formulas and ^{1}H NMR spectra with those of **1** and **2**. The biotransformed products (**11**, **12**, **13**) did not show any meaningful activity against drug-resistant strains of *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Enterococcus faecalis* or *Escherichia coli*, and their antibacterial activity was not examined further.



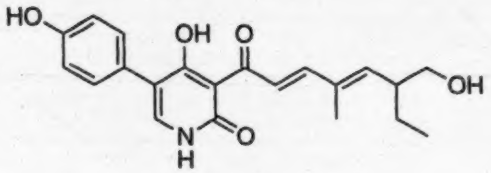
11 **12** **13**

Figure 4 Structures of **11**, **12**, and **13**

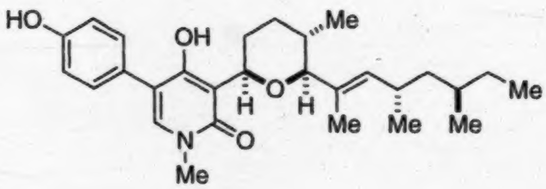
1.2 Recent studies on naturally-occurring 4-hydroxy-2-pyridinone compounds

Recently, several natural products related to the 4-hydroxy-2-pyridinone compounds **5-8**, such as pyridovericin[11,12] (**14**) and sambutoxin[13] (**15**), were synthesized by chemical methods.

Curran *et al.*[11] synthesized pyridovericin in both racemic and enantiomerically pure forms. His synthetic route is shown in Scheme 1. Monosilylation of 2-ethyl-1,3-propane diol (**1.1**) with *i*-Pr_3SiCl gave **1.2** in 98% yield. Swern oxidation and Wittig olefination then provided unsaturated



14

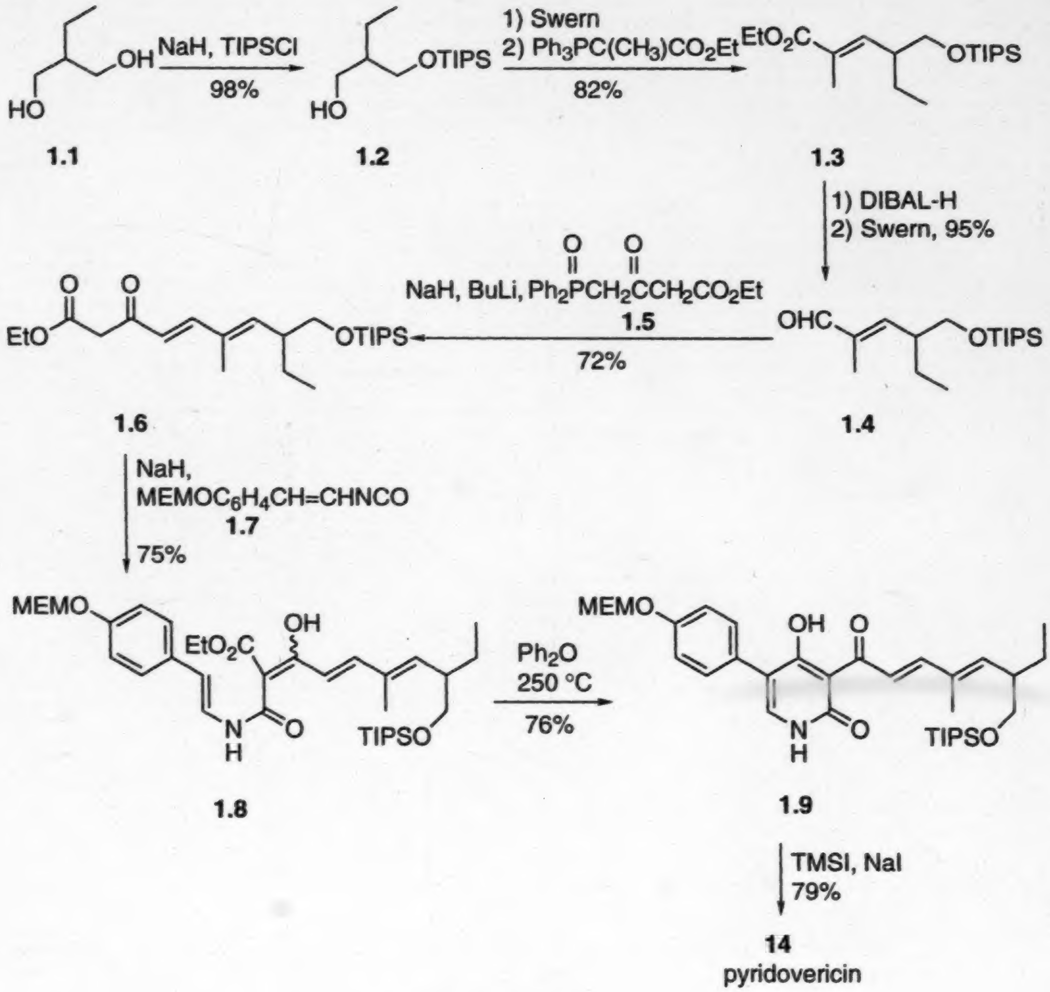


15

Figure 5 Structures of pyridovericin (**14**) and sambutoxin (**15**)

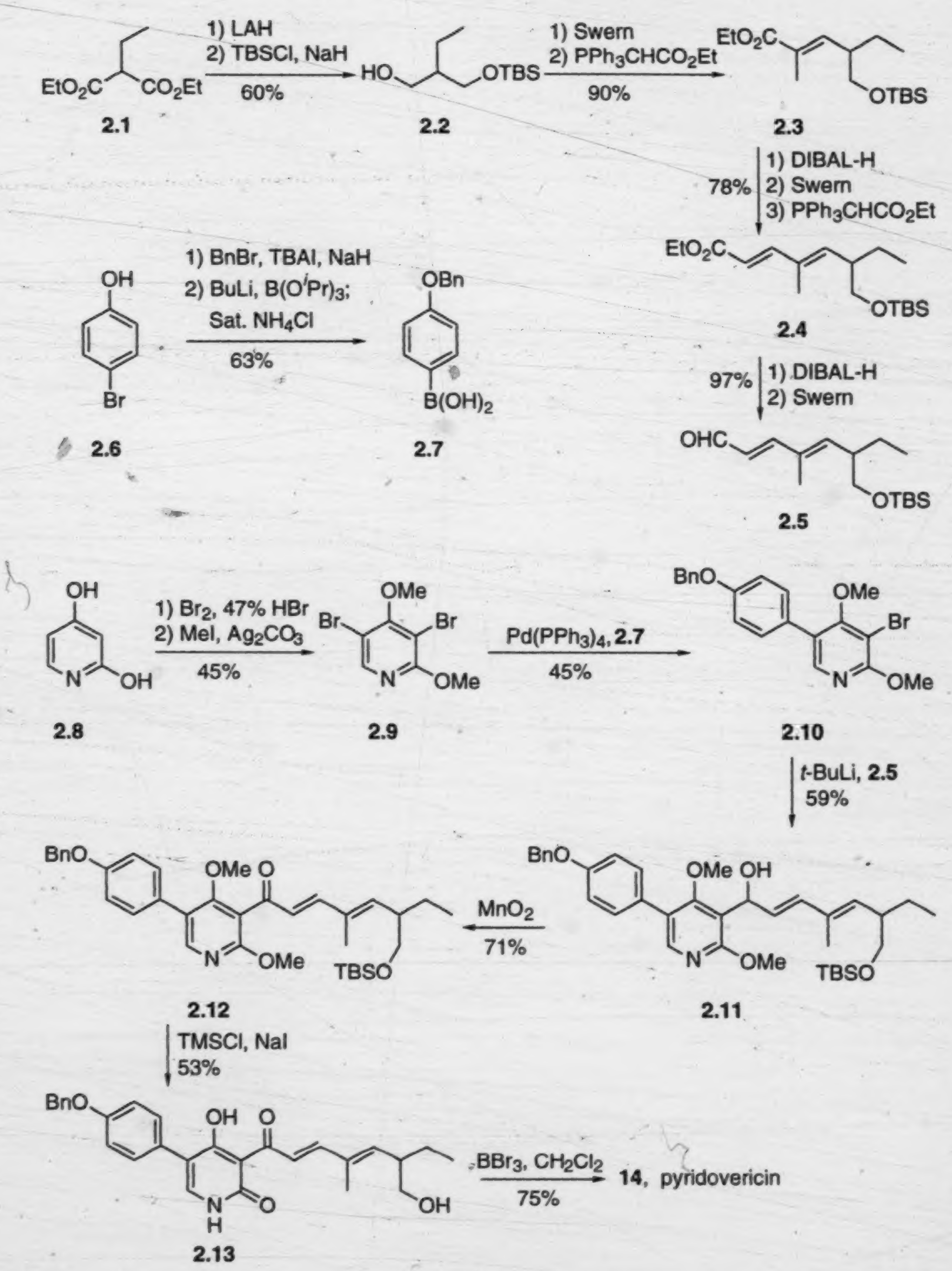
ester **1.3** in 82% yield, the material being >97% *E*-isomer. DIBAL-H reduction and Swern oxidation afforded aldehyde **1.4**, and this was subjected to olefination with phosphine oxide **1.5** to give β-ketoester **1.6** in 72% yield as a mixture of keto and enol forms (enol form not shown). Ketoester **1.6** was condensed with the readily available isocyanate **1.7** to produce enamide **1.8**, which exists in the enol form as shown, although the geometry of the enol double bond was not established. When **1.8** was heated for 5 min at 250 °C in Ph_2O the pyridinone **1.9** was obtained in 76% yield. Prolonged exposure of **1.9** to a large excess of Me_3SiCl and NaI served to remove both the *i*-Pr_3Si- and the MEM groups, thereby releasing the natural product **14** in 79% overall yield.

Baldwin[12] synthesized pyridovericin (Scheme 2) in a totally different way by using readily available 2,4-


NaH, TIPSCl
98%
1) Swern
2) $Ph_3PC(CH_3)CO_2Et$
82%
1) DIBAL-H
2) Swern, 95%
NaH, BuLi, $Ph_2PCH_2CCH_2CO_2Et$
1.5
72%
NaH,
$MEMOC_6H_4CH=CHNCO$
1.7
75%
Ph_2O
250 °C
76%
TMSI, NaI
79%
OH
HO
OTIPS
EtO_2C
OHC
EtO
MEMO
TIPSO
N
H
1.1
1.2
1.3
1.4
1.6
1.8
1.9
14
pyridovericin

Scheme 1

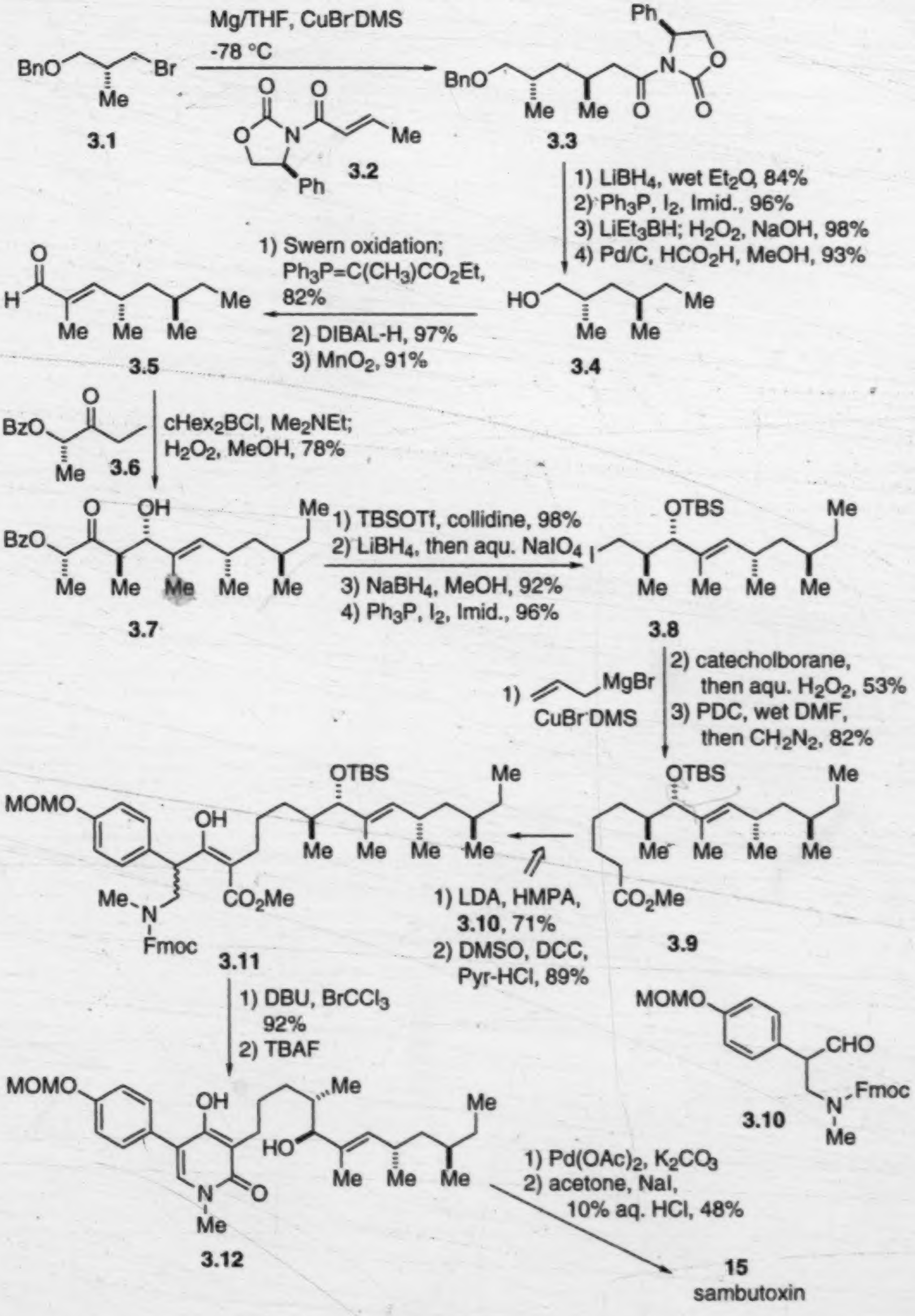
dihydroxypyridine as the eventual 2-pyridinone moiety in the natural product. Coupling of pyridine **2.9** with boronic acid **2.7** under Suzuki-type conditions afforded **2.10** (45%) as the major product, as well as two other byproducts. Metal-halogen exchange of **2.10**, followed by treatment with aldehyde **2.5** [made from diethyl 1-ethylmalonate (**2.1**)] gave (59%) the desired alcohol **2.11**. Oxidation of alcohol **2.11** with MnO_2


1) LAH
2) TBSCl, NaH
60%
2.1
2.2
1) Swern
2) PPh3CHCO2Et
90%
2.3
78%
1) DIBAL-H
2) Swern
3) PPh3CHCO2Et
2.4
97%
1) DIBAL-H
2) Swern
2.5
1) BnBr, TBAI, NaH
2) BuLi, B(O^iPr)3;
Sat. NH4Cl
63%
2.6
2.7
1) Br2, 47% HBr
2) MeI, Ag2CO3
45%
2.8
2.9
Pd(PPh3)4, 2.7
45%
2.10
t-BuLi, 2.5
59%
2.11
MnO2
71%
2.12
TMSCl, NaI
53%
2.13
BBr3, CH2Cl2
75%
14, pyridovericin

Scheme 2

afforded the fully protected pyridovericin **2.12** in good yield. *In situ* generated Me_3SiI removed the methyl ether and the silyl protecting groups, and removal of the benzyl group was effected with BBr_3 to generate racemic pyridovericin **14**. This route has thirteen steps in its longest linear sequence.

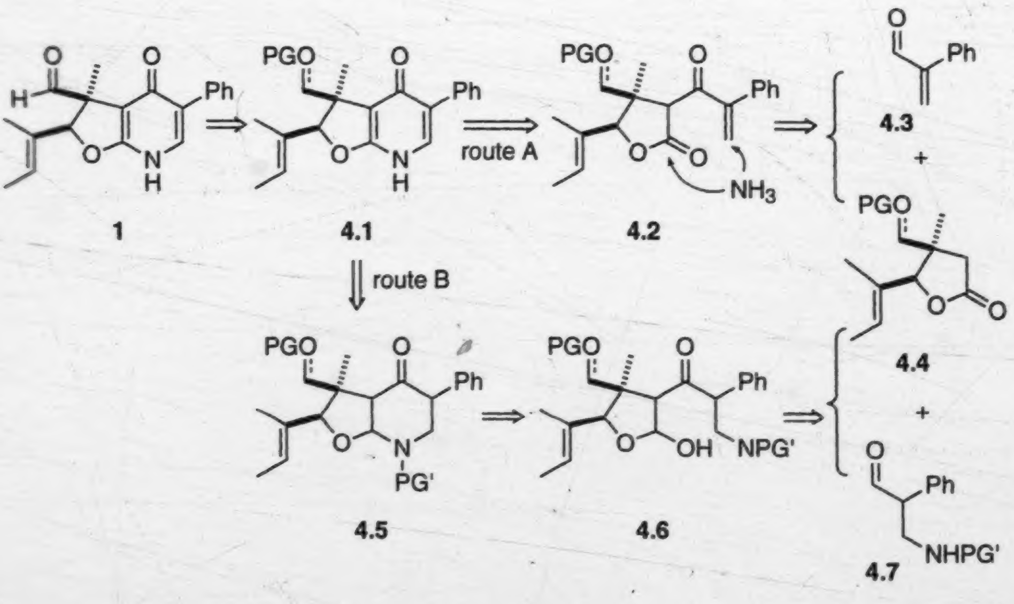
Total synthesis of sambutoxin[13] was achieved by Williams and Turske. The advanced intermediate **3.9** was made from bromide **3.1** by two asymmetric alkylations (**3.1** → **3.3**, **3.5** → **3.7**) (Scheme 3). Coupling of **3.9** with aldehyde **3.10** (made from the corresponding β-amino ester), followed by oxidation of the resulting alcohol, provided enol ester **3.11**. Removal of the Fmoc protecting group with DBU triggered spontaneous cyclization to an intermediate 5,6-dihydropyridinone, which underwent oxidation *in situ* to the pyridinone (cf. **3.12**) upon addition of $BrCCl_3$. The overall yield for Fmoc removal, spontaneous cyclization and oxidation was 92%. Removal of the *t*-$BuMe_2Si$ group with Bu_4NF provided the key intermediate **3.12**. Oxidation under buffered Saegusa conditions with $Pd(OAc)_2$ led to formation of the tetrahydropyran segment, and hydrolytic deprotection of the MOM group afforded sambutoxin **15**.


Mg/THF, CuBr·DMS
-78 °C
BnO
Br
Me
3.1
3.2
Ph
Me
3.3
1) LiBH$_4$, wet Et$_2$O, 84%
2) Ph$_3$P, I$_2$, Imid., 96%
3) LiEt$_3$BH; H$_2$O$_2$, NaOH, 98%
4) Pd/C, HCO$_2$H, MeOH, 93%
HO
3.4
1) Swern oxidation; Ph$_3$P=C(CH$_3$)CO$_2$Et, 82%
2) DIBAL-H, 97%
3) MnO$_2$, 91%
H
3.5
BzO
3.6
cHex$_2$BCl, Me$_2$NEt; H$_2$O$_2$, MeOH, 78%
OH
3.7
1) TBSOTf, collidine, 98%
2) LiBH$_4$, then aqu. NaIO$_4$
3) NaBH$_4$, MeOH, 92%
4) Ph$_3$P, I$_2$, Imid., 96%
OTBS
I
3.8
1) MgBr CuBr·DMS
2) catecholborane, then aqu. H$_2$O$_2$, 53%
3) PDC, wet DMF, then CH$_2$N$_2$, 82%
CO$_2$Me
3.9
1) LDA, HMPA, 3.10, 71%
2) DMSO, DCC, Pyr-HCl, 89%
MOMO
CHO
N
Fmoc
3.10
3.11
1) DBU, BrCCl$_3$ 92%
2) TBAF
3.12
1) Pd(OAc)$_2$, K$_2$CO$_3$
2) acetone, NaI, 10% aq. HCl, 48%
15
sambutoxin

Scheme 3

2 RESULTS AND DISCUSSION

By examining the structure of cladobotryal (**1**), we identified two main challenges to the total synthesis. The first problem was to generate the two contiguous stereogenic centers in the dihydrofuran ring, and the fact that one of these is a quaternary carbon center was likely to make this task difficult. The second challenge was to generate the 4-pyridinone ring system. We worked on two main plans; in the event, one of these allowed us to make cladobotryal. The other plan gave a 2-pyridinone product (cf. **5**, Figure 1); this also proved to be a synthetically useful result, since it provides a general approach to the synthesis of compounds **5**-**8** (Figure 1) and their analogs. As chance would have it, these compounds **5**-**8** were reported a very short time after we had made the 2-pyridinone **8.6** (see later).



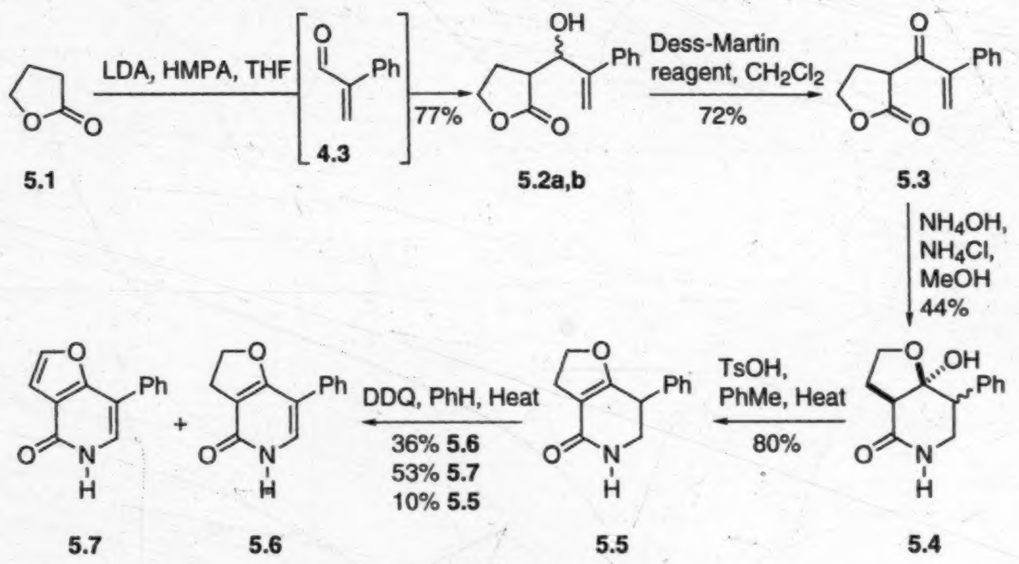
Scheme 4

The two routes we explored are shown on Scheme 4. We envisaged that the core structure of cladobotryal (**1**) could be generated by addition of ammonia to ketolactone **4.2**, giving precursor **4.1**, after oxidation (route A). The ketolactone **4.2** was judged to be accessible from lactone **4.4** (the symbol PGO= stands for a protected alcohol or protected aldehyde) and aldehyde **4.3**.[14] We felt that compound **4.1** could also be made by dehydrogenation of **4.5** (route B). The precursor (**4.6**) of **4.5** could be available by alkylation of the same lactone as in route A (**4.4**) with aldehyde **4.7**. Both routes were explored, route A gave a 2-pyridinone (2-*epi*-CJ-16,170), but route B led to the intended target, cladobotryal.

During my research it proved difficult to distinguish between 2- and 4-pyridinone systems by spectroscopic methods, and we actually made the core of CJ-16,170 (route A of Scheme 4) first, but its structure was not determined until we had made 2-*epi*-CJ-16,170, and had established the identity of that substance. With these reference samples of 2-pyridinones then in hand, we next prepared the core of cladobotryal, and finally, cladobotryal itself.

2.1 Synthesis of model compound 5.6, representing the core of CJ-16,170

Compound **5.6** was prepared by the route shown in Scheme 5. Deprotonation of γ-butyrolactone (**5.1**) and condensation with the known aldehyde **4.3**[14] gave **5.2** as a mixture of two


LDA, HMPA, THF
4.3
77%
OH
Ph
Dess-Martin
reagent, CH_2Cl_2
72%
5.1
5.2a,b
5.3
NH_4OH,
NH_4Cl,
MeOH
44%
TsOH,
PhMe, Heat
80%
DDQ, PhH, Heat
36% 5.6
53% 5.7
10% 5.5
5.7
5.6
5.5
5.4

Scheme 5

diastereoisomers in 77% yield, and Dess-Martin oxidation then afforded the derived ketone **5.3** (72%), which exists largely in the keto form shown (keto:enol = ca 9:1). Treatment with aqueous ammonia in MeOH in the presence of ammonium chloride brought about a number of changes that resulted in isolation of the chromatographically inseparable lactams **5.4** in 44% total yield. Evidently, Michael addition of ammonia, cyclization of nitrogen onto the lactone carbonyl to release a hydroxyethyl pendant, and cyclization of the latter onto the remaining ketone carbonyl took place. The lactams **5.4** were subjected to acid catalyzed dehydration by heating a PhMe solution in the presence of TsOH (**5.4** → **5.5**, 80% yield). Finally, dehydrogenation with DDQ in refluxing PhH gave **5.6** (36%), which represents the core of structures **5**-**8**. The product of further dehydrogenation (**5.7**, 53%), and some

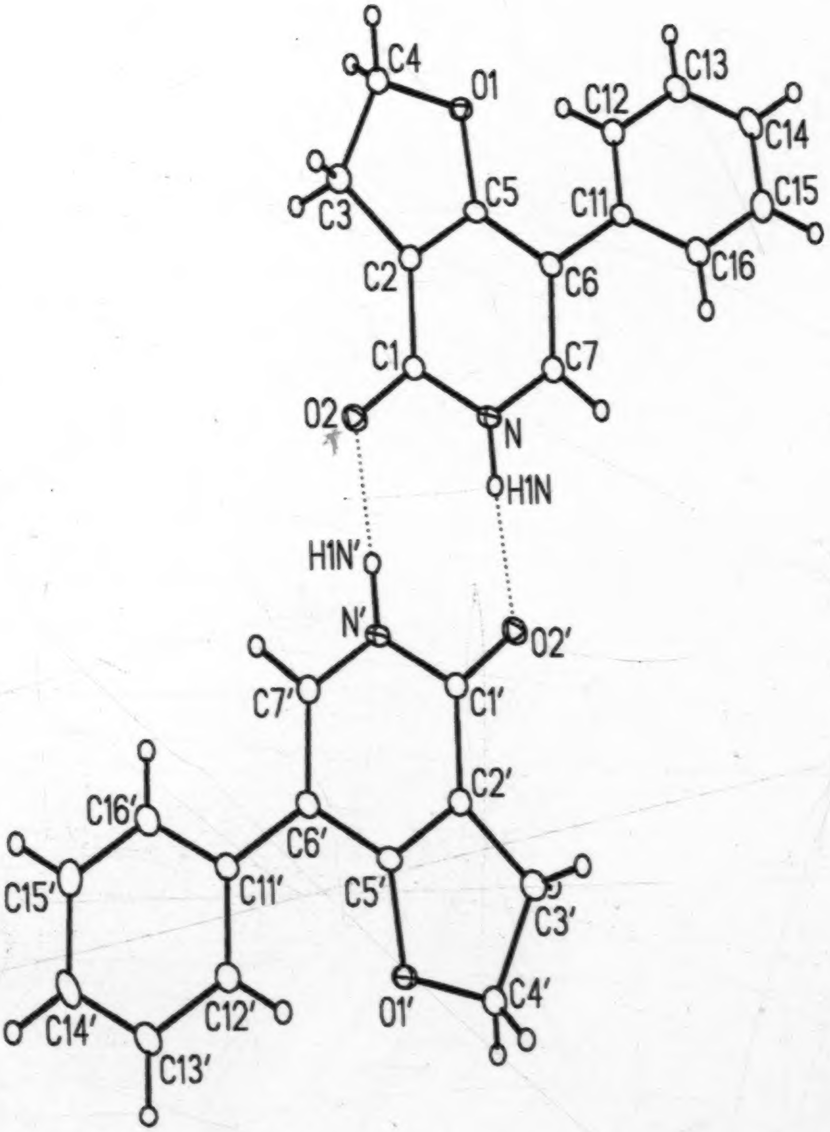

C4
O1
C12
C13
C14
C3
C5
C11
C15
C2
C6
C16
C1
C7
O2
N
H1N
H1N′
N′
O2′
C7′
C1′
C2′
C16′
C6′
C15′
C11′
C5′
C3′
O1′
C4′
C12′
C14′
C13′

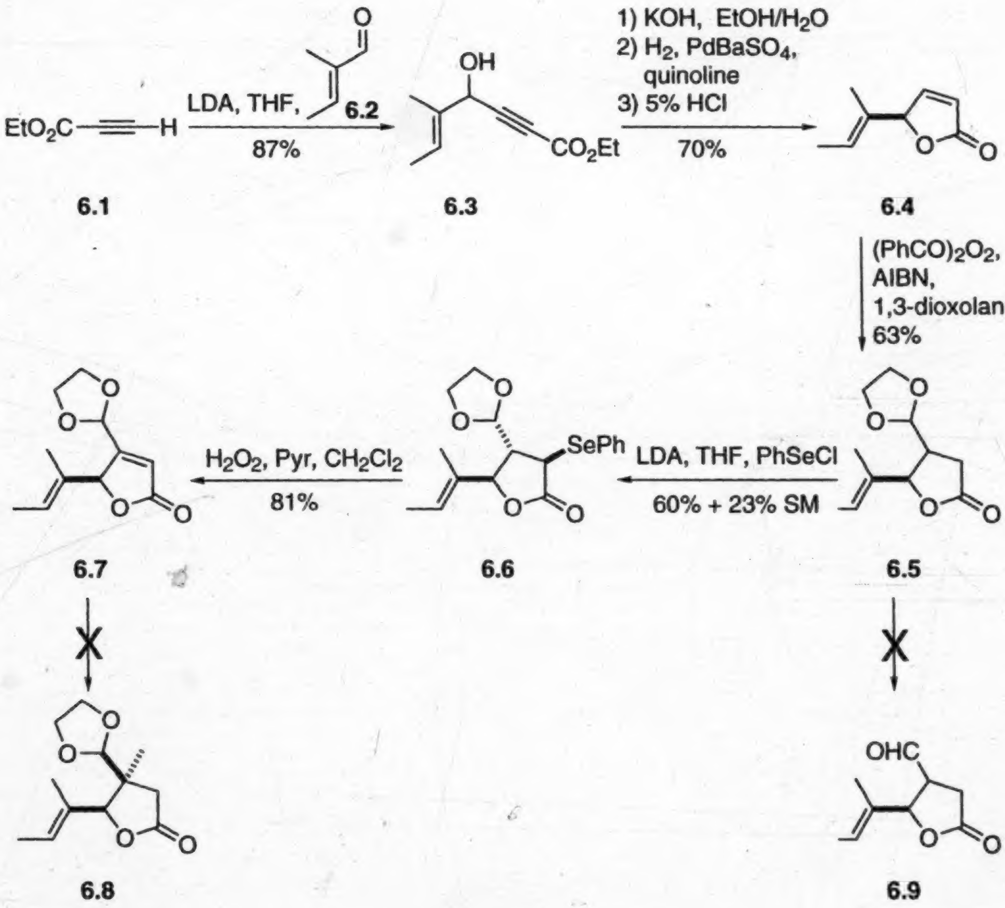
Figure 6 Crystal structure of **5.6**

unreacted starting material **5.5** (10%) were also isolated. The structure of **5.6** was established by single crystal X-ray analysis (see Experimental Section), which showed that the crystalline material exists in the pyridinone form (Figure 6).

2.2 Synthesis of 2-*epi*-CJ-16,170

a. Synthesis of lactone species (cf. **4.4***).*

We first examined the possibility of making lactone **6.8** (Scheme 6). Alkylation[15,16] of ethyl propiolate (**6.1**) with tiglic aldehyde (**6.2**) in the presence of LDA gave the desired alcohol **6.3** in 87% yield, and basic hydrolysis afforded the derived acid. This underwent hydrogenation in the presence of Lindlar catalyst and, when the reaction mixture was acidified with dilute (5%) hydrochloric acid, the α,β-unsaturated lactone **6.4** was produced in 70% overall yield.[16] Radical 1,4-addition of 1,3-dioxolane to the α,β-unsaturated lactone **6.4** was achieved by treatment of **6.4** with $(PhCO)_2O_2$ and AIBN using 1,3-dioxolane as solvent.[17] Regeneration of the double bond, as in **6.7**, was achieved by a standard two-step sequence: phenylselenation of **6.5** using LDA as the base gave **6.6**, and selenoxide elimination upon treatment with H_2O_2 and pyridine produced **6.7**. Unfortunately, all attempts, including both ionic and radical methods, to introduce the methyl group (**6.7** → **6.8**) were unsuccessful. These methods included the use of Me_2CuLi; $Me_2CuCNLi_2$; $Me_2CuLiSMe_2$; CH_2N_2;[18] CH_3NO_2, tetramethylguanidine; MeOH, $Ph_2C{=}O$, light; MeI,


6.1
LDA, THF, 6.2
87%
6.3
1) KOH, EtOH/H2O
2) H2, PdBaSO4, quinoline
3) 5% HCl
70%
6.4
(PhCO)2O2, AIBN, 1,3-dioxolane
63%
6.5
LDA, THF, PhSeCl
60% + 23% SM
6.6
H2O2, Pyr, CH2Cl2
81%
6.7
6.8
6.9
OHC
SePh
OH
CO2Et
EtO2C
H

Scheme 6

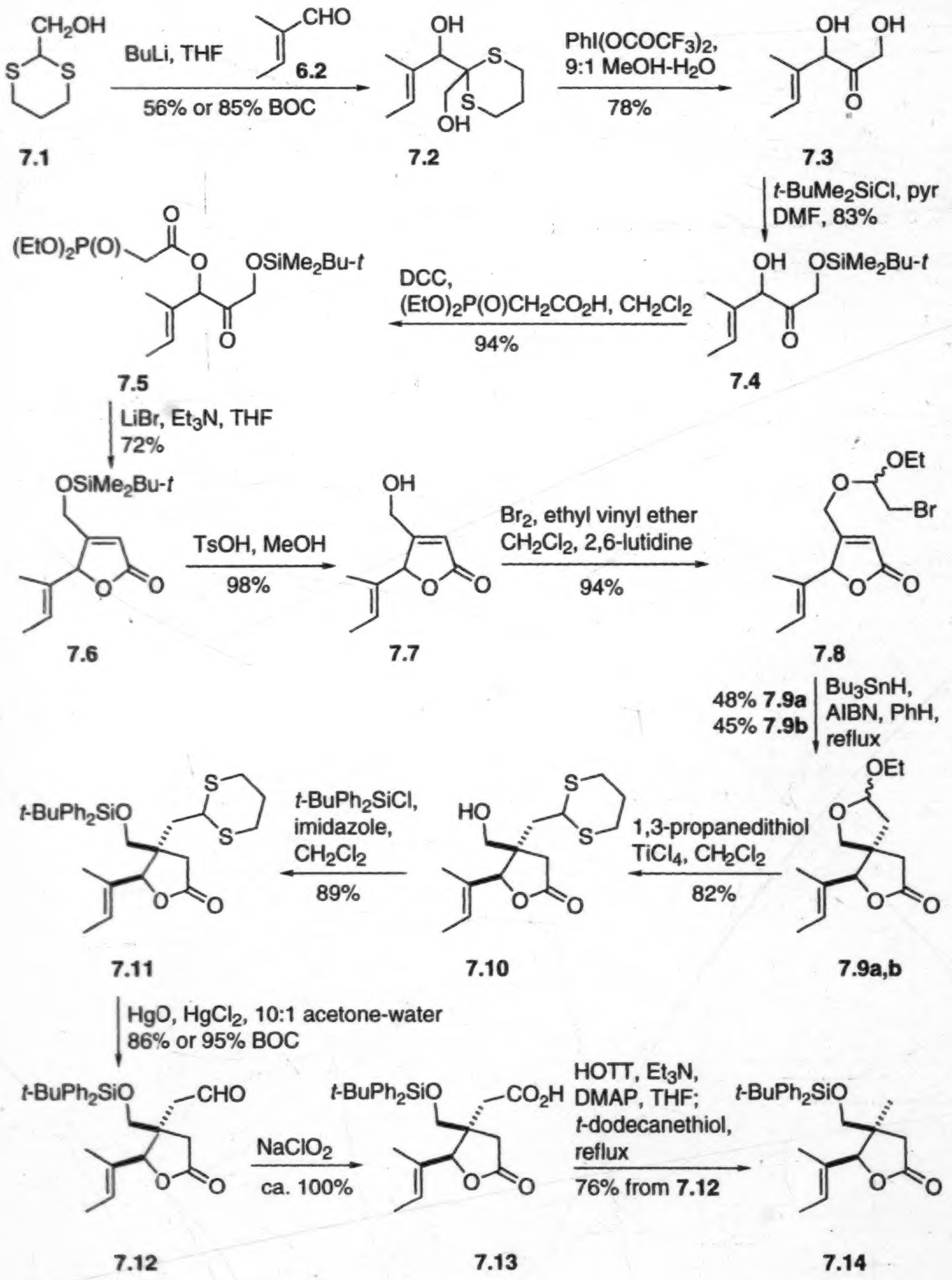
Bu_3SnCl, $NaBH_4$, EtOH, light; MeI, Ph_3SnH, Et_3B, air; $Me_3S{=}O$, DMSO, NaH.

Hydrolysis of acetal **6.5**, followed by alkylation of the derived aldehyde **6.9**, could possibly have given the desired lactone with the quaternary center (cf. **6.8**). Unfortunately, the hydrolysis could not be accomplished, although a variety of conditions were used. They included: PPTS, acetone; AcOH, water, 50 °C; 2 N hydrochloric acid, THF; TsOH, acetone, water, heat; HBF_4, MeCN; BBr_3, CH_2Cl_2; NaI, Me_3SiCl,

MeCN; DDQ, MeCN, water; CAN, 2,6-pyridinedicarboxylic acid *N*-oxide, MeCN; TFA, 6 N hydrochloric acid; concentrated hydrochloric acid, CH_2Cl_2; BCl_3, CH_2Cl_2; HIO_4, water; TFA, water.

These observations forced us to find an alternative way of making the required lactone species (cf. **4.4**). Eventually, a route was found, and is summarized in Scheme 7.

Double deprotonation of the known dithioacetal **7.1**[19] using BuLi, and condensation with tiglic aldehyde (**6.2**) gave alcohol **7.2** [56%, or 85% after correction for recovered **7.1** (34%)]. Hydrolysis of the dithiane unit to regenerate the carbonyl was achieved in 78% yield with $PhI(OCOCF_3)$[20] in aqueous MeOH, and afforded the dihydroxyketone **7.3**. The primary hydroxyl group could be protected selectively (**7.3** → **7.4**, *t*-$BuMe_2SiCl$, pyridine, DMF, 83%) and DCC-mediated acylation with diethylphosphonoacetic acid (**7.4** → **7.5**, 94%) then set the stage for an intramolecular olefination. This was accomplished (72%) by treating **7.5** with LiBr and Et_3N.[21] Deprotection of the silyl group of the resulting lactone (**7.6**) using Bu_4NF in THF led to decomposition, but the required transformation was successful under mildly acidic conditions ($TsOH.H_2O$, MeOH, 98%) so that the hydroxymethyl lactone **7.7** could be obtained. Conversion to the derived Stork bromoacetals (**7.7** → **7.8**) required extensive optimization, but we eventually found conditions that are very effective. Treatment of ethyl vinyl ether with Br_2, and addition of a solution of alcohol **7.7** and an excess of 2,6-


7.1
BuLi, THF
6.2
56% or 85% BOC
7.2
PhI(OCOCF$_3$)$_2$, 9:1 MeOH-H$_2$O
78%
7.3
t-BuMe$_2$SiCl, pyr DMF, 83%
7.4
DCC, (EtO)$_2$P(O)CH$_2$CO$_2$H, CH$_2$Cl$_2$
94%
7.5
LiBr, Et$_3$N, THF
72%
7.6
TsOH, MeOH
98%
7.7
Br$_2$, ethyl vinyl ether CH$_2$Cl$_2$, 2,6-lutidine
94%
7.8
Bu$_3$SnH, AIBN, PhH, reflux
48% 7.9a
45% 7.9b
7.9a,b
1,3-propanedithiol TiCl$_4$, CH$_2$Cl$_2$
82%
7.10
t-BuPh$_2$SiCl, imidazole, CH$_2$Cl$_2$
89%
7.11
HgO, HgCl$_2$, 10:1 acetone-water
86% or 95% BOC
7.12
NaClO$_2$
ca. 100%
7.13
HOTT, Et$_3$N, DMAP, THF; t-dodecanethiol, reflux
76% from 7.12
7.14

Scheme 7

lutidine gave the desired acetals (**7.8**) in 94% yield. Under the same reaction conditions, except that Et_3N/DMAP[22] were used as the base instead of 2,6-lutidine, bromoacetals **7.8** were isolated in less than 50% yield. Addition of Bu_3SnH and AIBN over 3 h to a refluxing solution of acetals **7.8** in PhH resulted in very efficient radical cyclization, which occurred from the face opposite to the olefinic substituent on the lactone ring, and this mode of closure provided the correct relative stereochemistry of the two contiguous stereogenic centers in the natural product. The product (**7.9a**,**b**) was isolated as two separate diastereoisomers (48% of **7.9a** and 45% of **7.9b**) that differ in stereochemistry at the ethoxy-bearing carbon atom. The stereochemistry of these compounds was established by X-ray analysis of the minor isomer (**7.9b**) (Figure 7) and the fact that both compounds ultimately lead to the same alcohol **7.10**. Treatment of **7.9a**,**b** with 1,3-propanedithiol in the presence of $TiCl_4$ at -20 °C gave dithioacetal **7.10** in 82% yield, and the primary hydroxyl group was protected (89%) by silylation (**7.10** → **7.11**), using *t*-$BuPh_2SiCl$ and imidazole. Then the latent aldehyde group was released by hydrolyzing the thioketal unit in the presence of mercuric ion (**7.11** → **7.12**); the yield in this process being 95% after correction for recovered **7.11** (ca 10%). Hydrolysis of the thioketal did not work well with PIFA, in contrast to the reaction **7.2** → **7.3**.

In order to convert the CH_2CHO substituent of **7.12** into a methyl group (see **7.14**), the aldehyde was treated with

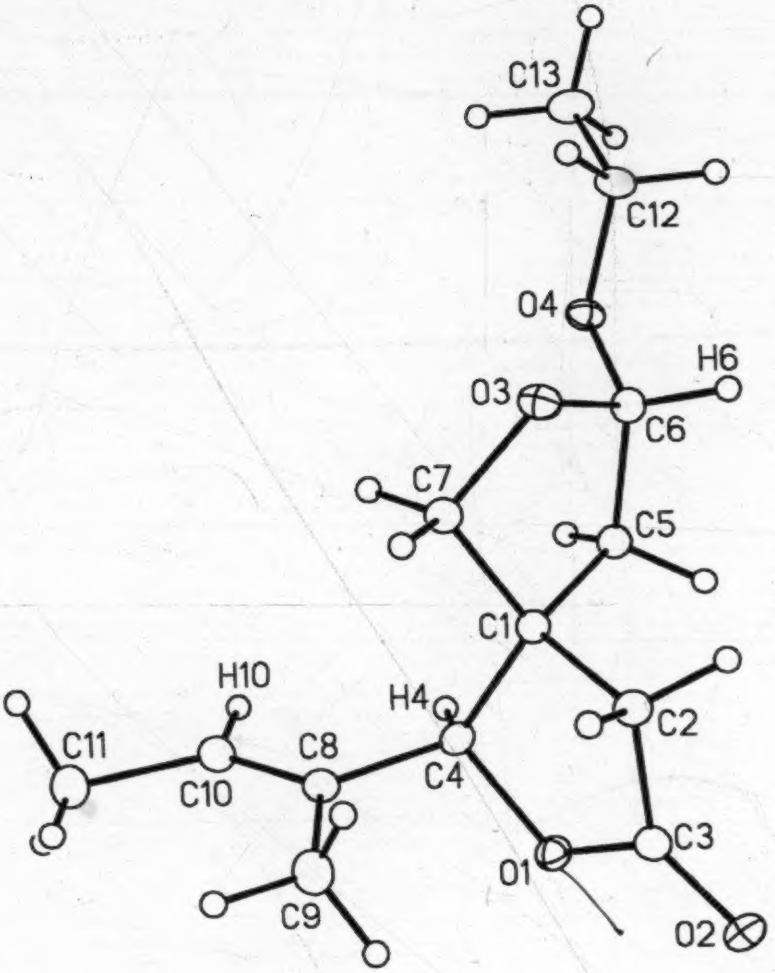

C13
C12
O4
H6
O3
C6
C7
C5
C1
H10
H4
C2
C11
C8
C10
C4
C3
O1
C9
O2

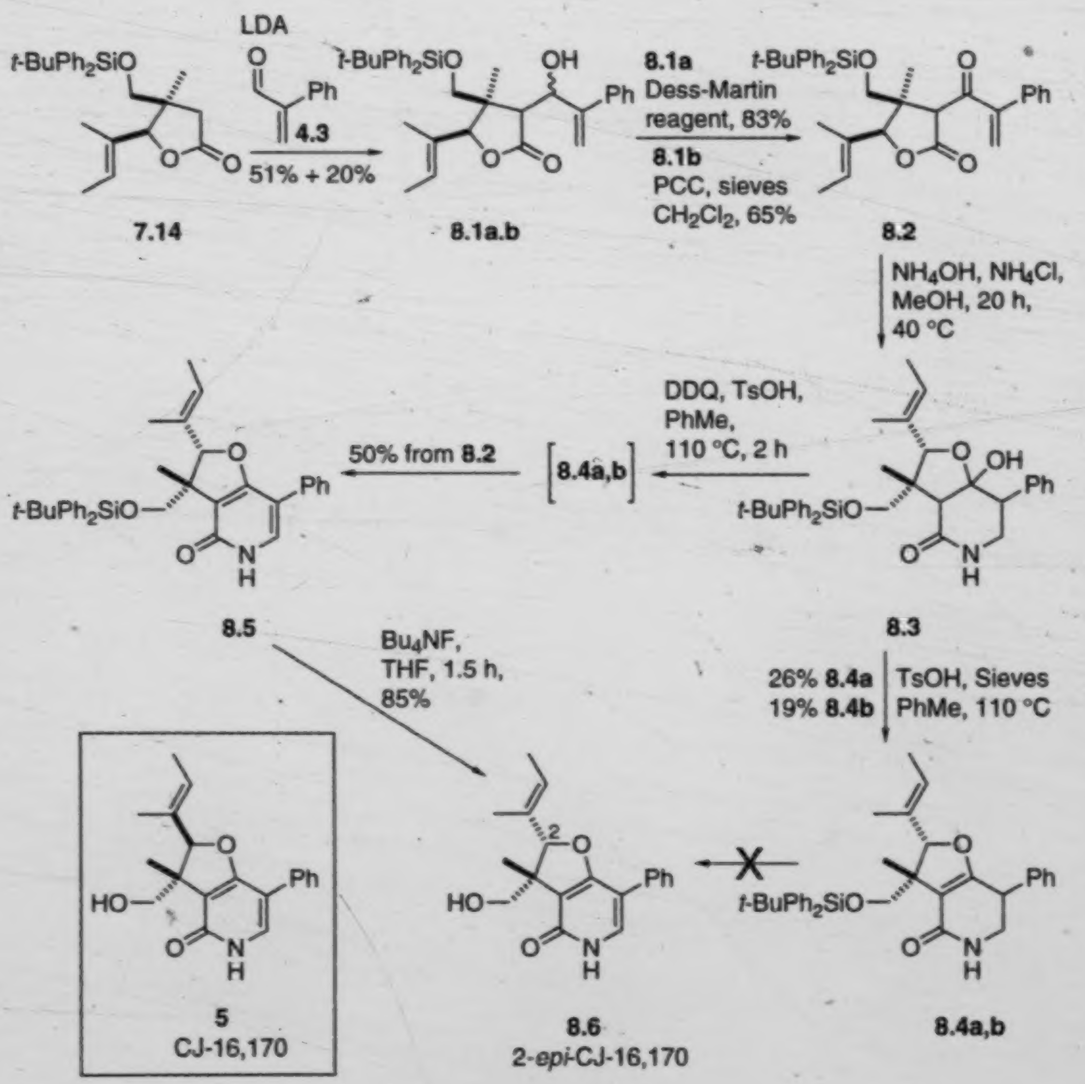
Figure 7 Crystal Structure of **7.9b**

✓

Wilkinson's catalyst[23] [$RhCl(PPh_3)_3$, 1 equiv] in CH_2Cl_2 to afford the desired product **7.14**, but the yield was only ca 8%. The required transformation was eventually achieved by a two step sequence. Aldehyde **7.12** was oxidized quantitatively to the corresponding acid (**7.12** → **7.13**), in the usual way ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene), and the acid was then converted into its Barton ester. Under standard conditions [(a) *N*-hydroxypyridine-2-thione, DMAP, DCC in PhMe; (b) Bu_3SnH, AIBN in refluxing PhH][24] the yield was low, but when the reagent HOTT[25] was used to form the Barton ester (with protection from light) the efficiency was greatly increased, and heating the resulting ester in the presence of *t*-dodecanethiol, now without protection from light, gave the desired lactone **7.14** in 76% yield, and this step completed the generation of the desired relative stereochemistry at the two contiguous stereogenic centers.

b. Synthesis of 2-epi-CJ-16,170

With lactone **7.14** in hand, we applied a similar reaction sequence to that used in our model study leading to the core structure **5.6** (Scheme 5). Lactone **7.14** was deprotonated at 0 °C (LDA, THF), and the enolate was allowed to react at -78 °C with the known aldehyde **4.3**.[14] The resulting alcohols (**8.1a**,**b**) were obtained as two separable diastereoisomers (51% for **8.1a** and 20% for **8.1b**). The major diastereoisomer (**8.1a**) was oxidized to enone **8.2** in 83% by using the Dess-Martin reagent in CH_2Cl_2. Dess-Martin oxidation of the minor



t-BuPh2SiO
7.14
LDA
4.3
Ph
51% + 20%
OH
8.1a.b
8.1a
Dess-Martin reagent, 83%
8.1b
PCC, sieves
CH2Cl2, 65%
8.2
NH4OH, NH4Cl,
MeOH, 20 h,
40 °C
8.3
DDQ, TsOH,
PhMe,
110 °C, 2 h
8.4a,b
50% from 8.2
8.5
26% 8.4a
19% 8.4b
TsOH, Sieves
PhMe, 110 °C
8.4a,b
Bu4NF,
THF, 1.5 h,
85%
HO
8.6
2-epi-CJ-16,170
5
CJ-16,170
2

Scheme 8

diastereoisomer **8.1b** only led to decomposition, and the oxidation of **8.1b** was best done with PCC in the presence of 4 Å molecular sieves, and gave **8.2** in 65% yield. Exposure of **8.2** to aqueous ammonia in the presence of NH_4Cl in MeOH[26] at 40 °C for 20 h gave **8.3** for which the stereochemistry of the asymmetric centers on the six-membered ring was not

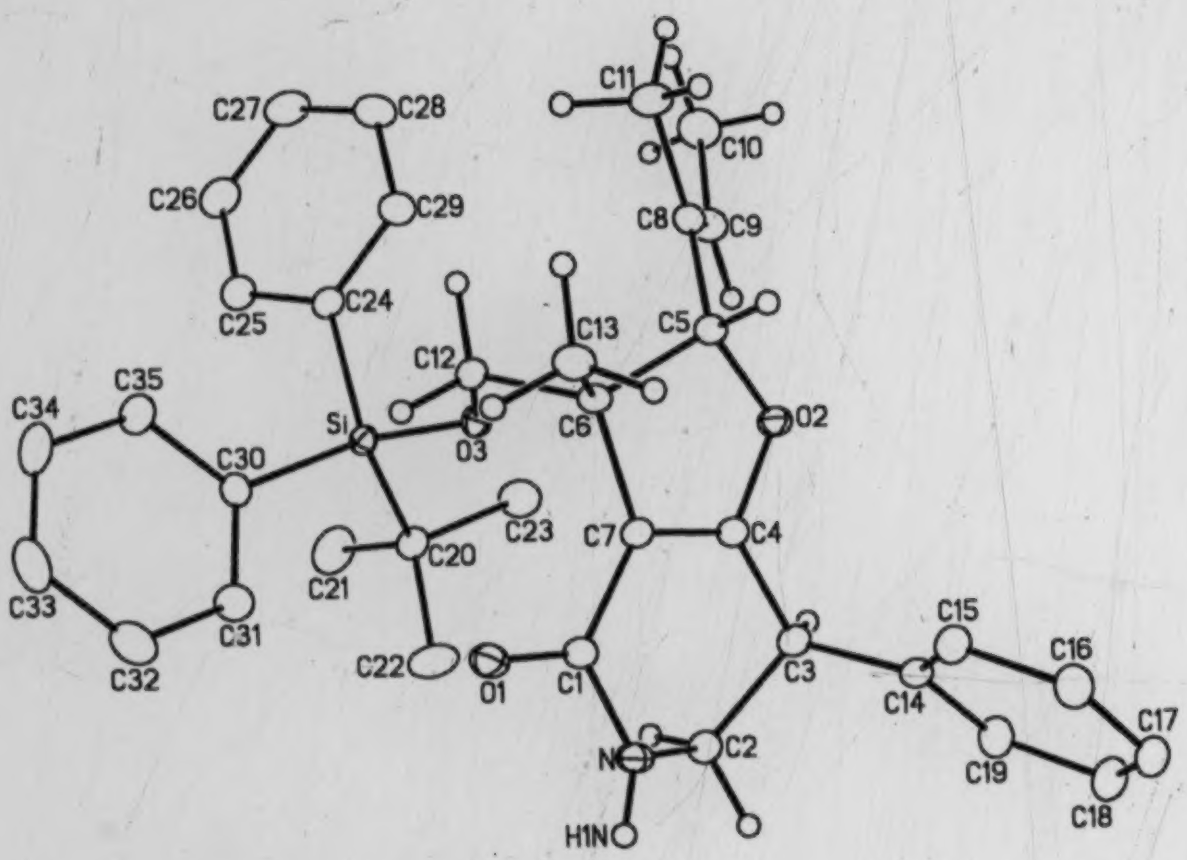

C11
C10
C27
C28
C26
C29
C8
C9
C25
C24
C13
C5
C12
C35
C34
Si
C6
O2
O3
C30
C23
C7
C4
C21
C20
C33
C31
C15
C16
C22
O1
C1
C3
C32
C14
C17
N
C2
C19
C18
H1N

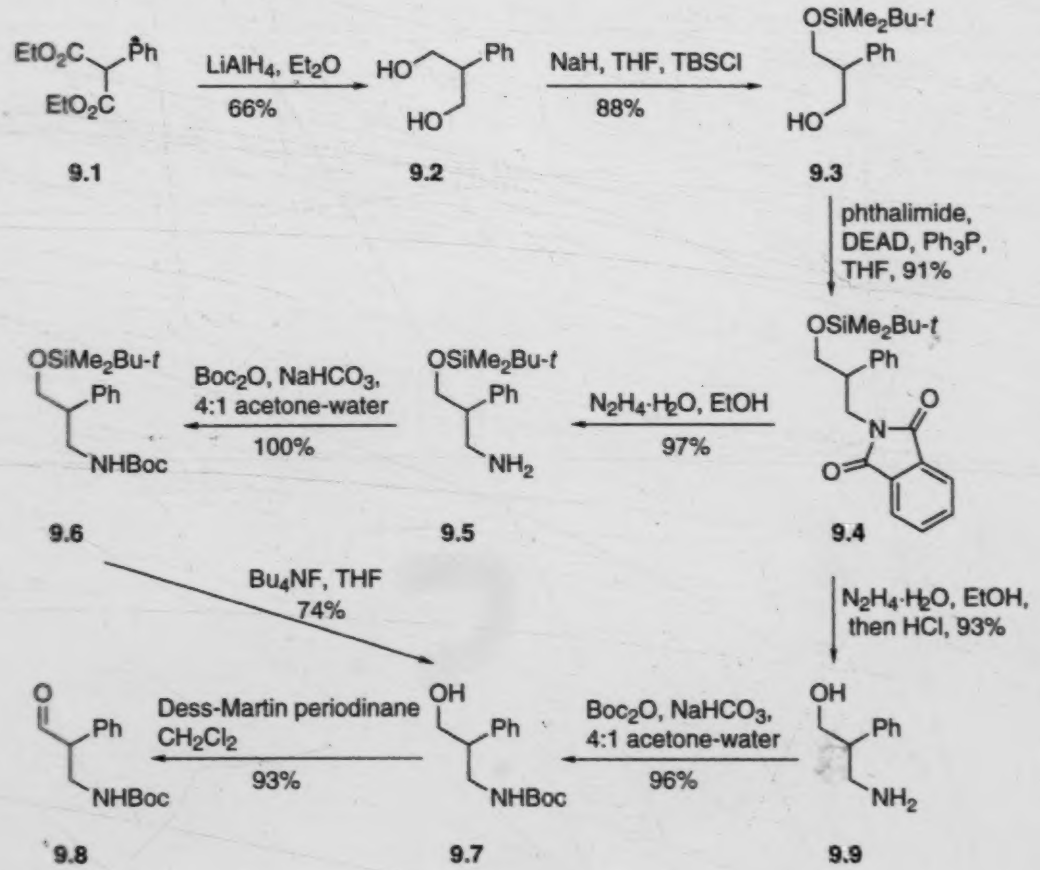
Figure 8 Crystal structure of 8.4a

determined. The crude material was heated with TsOH in refluxing PhMe in the presence of 4 Å molecular sieves, and the dehydration products **8.4** were isolated as two separable diastereoisomers (26% for **8.4a** and 19% for **8.4b**). The less polar (and major) diastereoisomer **8.4a** was recrystallized from EtOAc-hexane, and the structure was determined by X-ray analysis (Figure 8). An attempt to dehydrogenate **8.4a,b**, using DDQ alone, was not successful, and the same was true when we treated **8.4a,b** with CAN, thallium (III) *p*-toluenesulphonate[27] or TPAP.[28] Fortunately, when crude **8.3** was heated with DDQ in the presence of TsOH, dehydration (**8.3** → **8.4**) and acid-facilitated[29] dehydrogenation (**8.4** → **8.5**) occurred, and **8.5** was isolated in 50% overall yield from **8.2**. The presence of TsOH is essential in this dehydrogenation process. Finally, compound **8.6** was generated by desilylation of **8.5** in 85% yield using Bu_4NF. Compound **8.6** and the naturally-occurring CJ-16,170 (**5**) differ only in stereochemistry at C(2), and we call our material 2-*epi*-CJ-16,170.

The method used to make pyridinones **5.6** and **8.6** should be applicable to a number of derivatives, especially those in which the phenyl substituent has been modified, but we have not tested this possibility.

2.3 Synthesis of model compound 10.6, representing the core of cladobotryal

The route to **10.6** (see Scheme 10), which is the core of

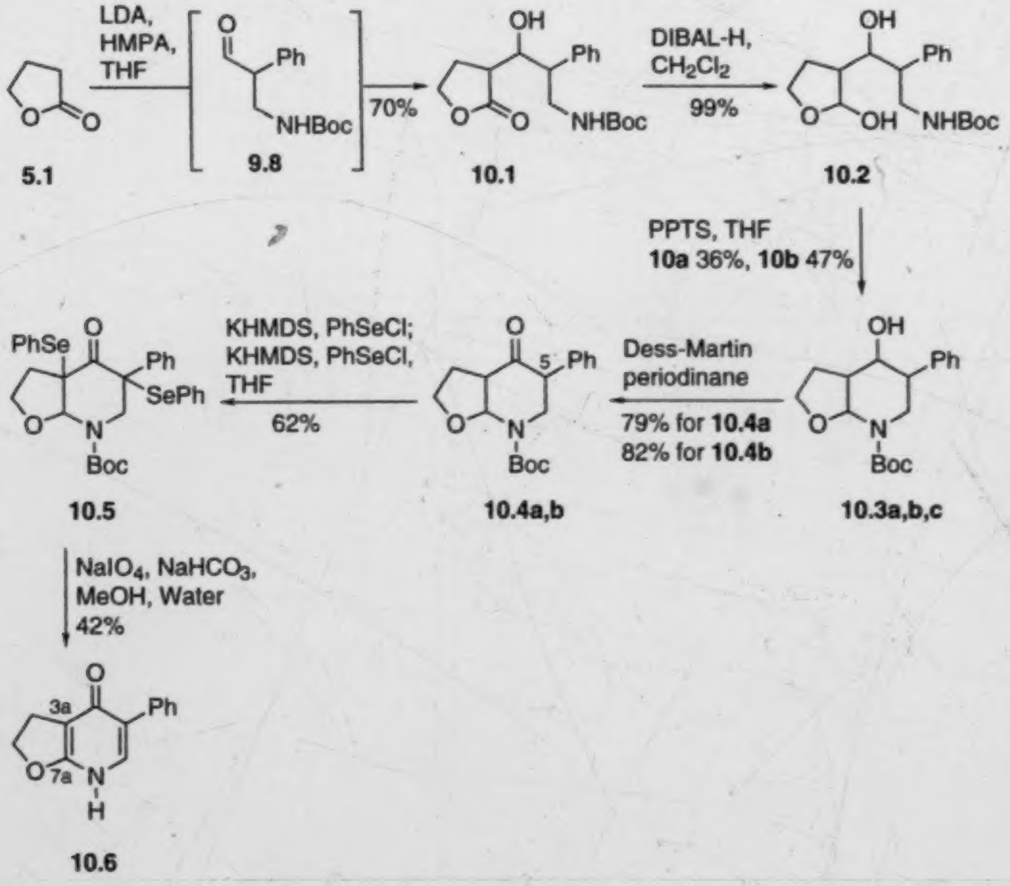

9.1
LiAlH4, Et2O
66%
9.2
NaH, THF, TBSCl
88%
9.3
phthalimide, DEAD, Ph3P, THF, 91%
9.4
N2H4·H2O, EtOH
97%
9.5
Boc2O, NaHCO3, 4:1 acetone-water
100%
9.6
Bu4NF, THF
74%
N2H4·H2O, EtOH, then HCl, 93%
9.9
Boc2O, NaHCO3, 4:1 acetone-water
96%
9.7
Dess-Martin periodinane CH2Cl2
93%
9.8

Scheme 9

cladobotryal, is based on the two subunits γ-butyrolactone (**5.1**) and the known[30] β-amino aldehyde **9.8**, which we made (Scheme 9) by the sequence **9.9** → **9.7** → **9.8**, along lines reported[30] in the literature, but with minor modifications. We found it convenient to prepare intermediate **9.9** by a different route from those previously reported.[30,31] Alcohol **9.3**,[32] was made from commercially available diethyl phenylmalonate (**9.1**) by $LiAlH_4$ reduction (66%) and monoprotection with *t*-$BuMe_2SiCl$ in 88% yield, following literature[32] procedures. Alcohol **9.3** was converted efficiently (91%) into the phthalimide **9.4** under Mitsunobu conditions (phthalimide, DEAD, Ph_3P), and treatment with $N_2H_4.H_2O$ in EtOH then liberated amine **9.5** (97%). This was protected quantitatively as its *N*-Boc derivative (**9.5** → **9.6**) using standard conditions (Boc_2O, aqueous acetone, $NaHCO_3$). Desilylation with Bu_4NF gave alcohol **9.7** (74%), and Dess-Martin oxidation (93%) afforded the required aldehyde **9.8**.

The same aldehyde was also made by a slightly shorter route in which phthalimide **9.4** was treated successively with $N_2H_4.H_2O$ and 5% hydrochloric acid to produce amino alcohol **9.9**[30,31] (93%), which was easily converted into **9.7**[30] (96%) by reaction with Boc_2O.

Deprotonation of γ-butyrolactone (**5.1**) and condensation (70%) with aldehyde **9.8** (Scheme 10) served to link the two subunits. The product (**10.1**) was obtained as a mixture of diastereoisomers. Reduction of the lactone carbonyl with DIBAL-H (**10.1** → **10.2**, 99%) then set the stage for the key ring closure (**10.2** → **10.3a**,**b**,**c**). This was accomplished efficiently (83%) by exposure to pyridinium *p*-toluenesulfonate at room temperature. Chromatography of the cyclization products gave two fractions; one was a single diastereoisomer (**10.3a**) and the other a mixture of two diastereoisomers (**10.3b**,**c**). The stereochemistry of the components of these fractions was not established, and the fractions were individually subjected to oxidation with the Dess-Martin reagent (ca 80% for each case) to produce a single ketone from each experiment. These ketones (**10.4a**,**b**)


LDA,
HMPA,
THF
Ph
NHBoc
70%
OH
Ph
NHBoc
DIBAL-H,
CH_2Cl_2
99%
OH
Ph
OH
NHBoc
5.1
9.8
10.1
10.2
PPTS, THF
10a 36%, 10b 47%
PhSe
Ph
SePh
Boc
KHMDS, PhSeCl;
KHMDS, PhSeCl,
THF
62%
5
Ph
Boc
Dess-Martin
periodinane
79% for 10.4a
82% for 10.4b
OH
Ph
Boc
10.5
10.4a,b
10.3a,b,c
$NaIO_4$, $NaHCO_3$,
MeOH, Water
42%
3a
Ph
7a
H
10.6

Scheme 10

differ in stereochemistry at C(5).

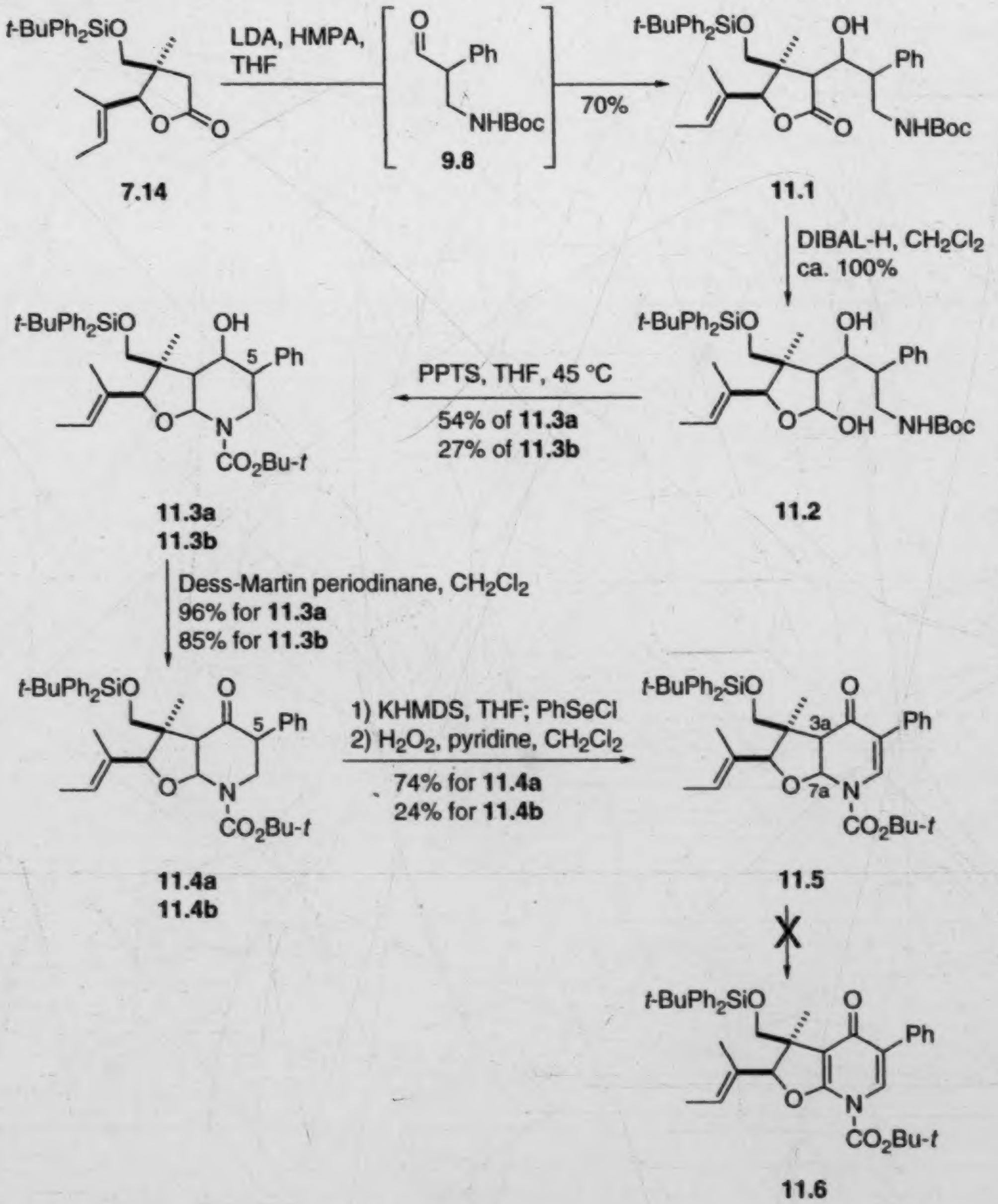
In order to introduce two double bonds into the six-membered ring (cf. **10.6**), a mixture of the ketones was deprotonated with $(Me_3Si)_2NK$ at 0 °C, treated with PhSeCl at -78 °C, deprotonated again *in situ* at 0 °C, and quenched once more at -78 °C with PhSeCl. This sequence of operations gave bis-selenides **10.5** as a mixture of diastereoisomers in 62% yield. The compounds were not fully characterized, but oxidized immediately with $NaIO_4$ in aqueous methanolic $NaHCO_3$.

Double selenoxide fragmentation of **10.5** occurred as well as loss of the Boc group, affording the desired core structure of cladobotryal (**10.6**) in 42% yield from **10.4a,b**.[33] We did not establish if the C(3a)-C(7a) double bond of **10.6** is formed directly in its final position or is the result of isomerization of an initially-formed 3,3a-double bond.[35]

2.4 Synthesis of racemic cladobotryal

In the work leading to **8.6**, we had condensed the substituted lactone **7.14** with the simple aldehyde **4.3** (see Scheme 8). Our route to cladobotryal is also convergent and is based on the same γ-lactone (**7.14**), which was destined to provide the dihydrofuran segment of the natural product (**1**).

We made many efforts to divert intermediates obtained from **7.14** and **4.3** (and also from **5.1** and **4.3**) into the cladobotryal system, but before we had exhausted our plans to this end, it had become clear that a successful route would be most easily found by using, instead of **4.3**, an aldehyde carrying both the phenyl substituent and a suitably protected nitrogen (or group that could be replaced by nitrogen) β to the carbonyl group. In the event, several such aldehydes had to be tried before we established through the model studies described above (see Scheme 9, 10) that **9.8** is a satisfactory aldehyde. In some of the aldehydes we examined, the nitrogen atom was protected with groups other than Boc, in one case nitrogen was present as an azide, and in some cases nitrogen was not present.


t-BuPh2SiO
LDA, HMPA, THF
O
Ph
NHBoc
9.8
70%
OH
7.14
11.1
DIBAL-H, CH2Cl2
ca. 100%
5
Ph
PPTS, THF, 45 °C
54% of 11.3a
27% of 11.3b
N
CO2Bu-t
OH
11.3a
11.3b
11.2
Dess-Martin periodinane, CH2Cl2
96% for 11.3a
85% for 11.4b
1) KHMDS, THF; PhSeCl
2) H2O2, pyridine, CH2Cl2
74% for 11.4a
24% for 11.4b
3a
7a
11.4a
11.4b
11.5
11.6

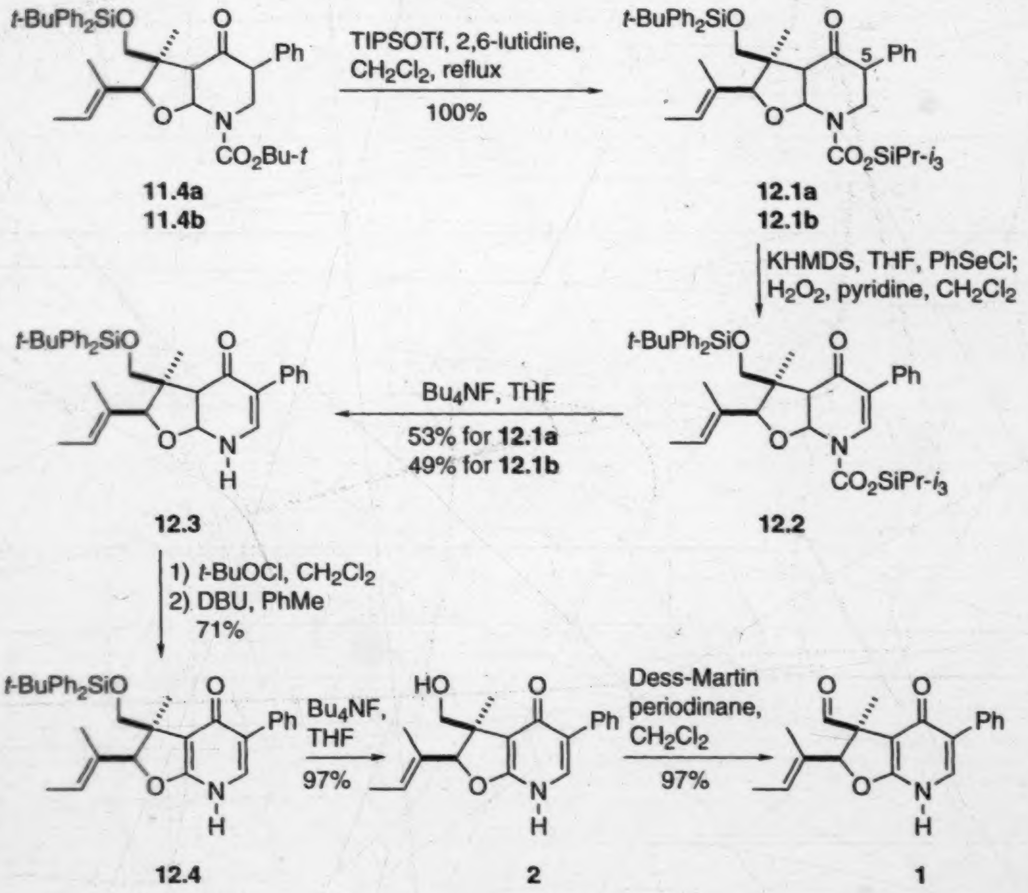
Scheme 11

Deprotonation of lactone **7.14** with 3 equiv LDA in THF, and addition of a THF solution of aldehyde **9.8** and HMPA (1.5 equiv) gave the expected condensation product **11.1** as a mixture of diastereoisomers in 71% yield. Some starting lactone (29%) was also recovered, so that the yield is 100%, after correction for recovered starting lactone (Scheme 11). DIBAL-H reduction of **11.1** generated the corresponding lactols **11.2** (ca 100%), and these could be cyclized in the required manner (**11.2** → **11.3**) under mildly acidic conditions by exposure to pyridinium *p*-toluenesulfonate. The product was isolated as two fractions, the chromatographically faster-moving fraction (**11.3a**) being obtained in 54% yield, and the slower-moving fraction (**11.3b**) in 27% yield. NMR measurements showed that each fraction was a single diastereoisomer, but the relative stereochemistry was not determined. Oxidation to the corresponding ketones was done with the Dess-Martin reagent (96% for **11.4a**; 85% for **11.4b**). Each ketone was a single diastereoisomer differing in stereochemistry at C(5).

Attempts to introduce both of the required double bonds were made with **11.4a**, and **11.4b** was not examined for this purpose. Double phenylselenation of **11.4a**, exactly as in the model series (cf. Scheme 10, **10.4a,b** → **10.5**), was not successful. However, introduction of the first of the required double bonds (**11.4a** and **11.4b** → **11.5**) was readily achieved with both ketones by phenylselenation [$(Me_3Si)_2NK$, THF, PhSeCl] and selenoxide fragmentation (H_2O_2, pyridine, CH_2Cl_2) [74% overall for **11.4a**, 24% (not optimized) for **11.4b**]. Unfortunately, the product **11.5** resisted further desaturation to **11.6**. Phenylselenation of **11.5** at C(3a) now proved impossible, using LDA or $(Me_3Si)_2NK$, followed by addition of PhSeCl, probably because severe steric crowding blocks access to C(3a). We did not do a control experiment to test if at least deprotonation was occurring. Phenylselenation of **11.5** after desilylation also failed. We then tried to introduce a PhSe group by selenation of lactone **7.14** before condensation with **9.8**. This approach should have given compounds with the PhSe group at the eventual C(3a) position; however, lactone reduction (cf. **11.1** → **11.2**, Scheme 11) after the condensation was accompanied by loss of the selenium group. Dehydrogenation of **11.5** using DDQ, Pd/C, MnO_2, $(NH_4)_2Ce(NO_3)_6$,[36] Ph_3CPF_6,[37] or $[PhSe(O)]_2O$, in some cases,[38] under a variety of conditions, was also unsuccessful.

At this stage, we considered that removal of the *N*-Boc group would provide an alternative method for introducing the C(3a)-C(7a) double bond (as described below), but attempts to deprotect the nitrogen of **11.5**, using CF_3CO_2H or bromocatecholborane, caused decomposition, and so we were forced to explore several modified versions of our route.

During these renewed efforts, we tried to protect the hydroxyl of **11.1** as its triisopropylsilyl ether (i-$Pr_3SiOSO_2CF_3$, 2,6-lutidine), but found instead that the Boc group was converted into a CO_2SiPr-i_3 group before the hydroxyl itself was silylated. The analogous conversion of *N*-Boc into *N*-$COOSiMe_2Bu$-*t* had in fact been observed before, with *t*-$BuMe_2SiOSO_2CF_3$,[39] although we were unaware of this reaction at the time. However, our own experimental


t-BuPh2SiO
O
Ph
O
N
CO2Bu-t
11.4a
11.4b
TIPSOTf, 2,6-lutidine,
CH2Cl2, reflux
100%
t-BuPh2SiO
O
5
Ph
O
N
CO2SiPr-i3
12.1a
12.1b
KHMDS, THF, PhSeCl;
H2O2, pyridine, CH2Cl2
t-BuPh2SiO
O
Ph
O
N
H
12.3
Bu4NF, THF
53% for 12.1a
49% for 12.1b
t-BuPh2SiO
O
Ph
O
N
CO2SiPr-i3
12.2
1) t-BuOCl, CH2Cl2
2) DBU, PhMe
71%
t-BuPh2SiO
O
Ph
O
N
H
12.4
Bu4NF,
THF
97%
HO
O
Ph
O
N
H
2
Dess-Martin
periodinane,
CH2Cl2
97%
O
O
Ph
O
N
H
1

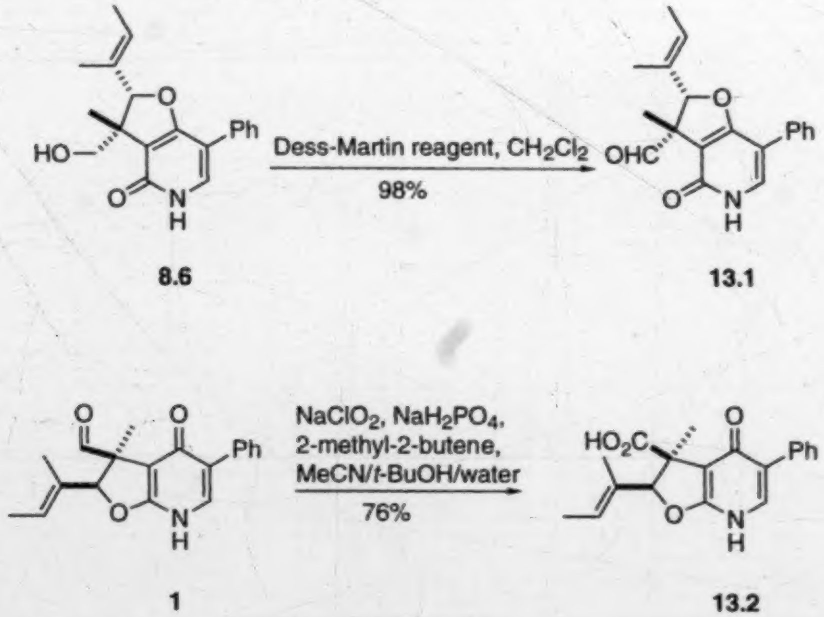
Scheme 12

observation prompted us to treat **11.4a** and **11.4b** with *i*-$Pr_3SiOSO_2CF_3$. In the event this was the key reaction that allowed us to bypass the barriers that had earlier thwarted introduction of the C(3a)-C(7a) double bond.

Both **11.4a** and **11.4b** were converted quantitatively into the silyl carbamates **12.1a** and **12.1b**, respectively, by treatment with *i*-$Pr_3SiOSO_2CF_3$ (Scheme 12). Each carbamate could be desaturated at C(5)-C(6) by phenylselenation and selenoxide elimination, under the conditions we had used to make **11.5**. The crude products (**12.2**) from **12.1a** and **12.1b** were identical, of course. The compounds were not very stable to chromatography over silica or alumina, but were not so fragile as to preclude further transformations. The nitrogen protecting group could now be removed under non-acidic conditions (Bu_4NF, THF) to afford **12.3** (53% overall from **12.1a**, 49% overall from **12.1b**). Compound **12.3**, which was stable to flash chromatography over silica gel, provided an opportunity to generate an imine that would be expected to tautomerize spontaneously to **12.4**. Several methods are available for converting a CH-NH unit into an imine,[40] but the classical procedure[40b] of *N*-chlorination (*t*-BuOCl)[41] and base treatment (DBU), with which other group members had had direct experience several years ago,[42] again proved satisfactory, and gave pyridinone **12.4** in 71% yield. Cladobotryal (**1**) was then easily reached via the natural product **2** by desilylation (Bu_4NF, THF, 97%) and Dess-Martin oxidation (**2** → **1**, 97%) (Scheme 12). The ^1H and ^{13}C NMR spectra of our racemic materials matched those reported for the natural products.

2.5 Derivatives of 2-*epi*-CJ-16,170 and cladobotryal

2-*epi*-CJ-16,170 (**8.6**) and cladobotryal (**1**) were both used to make derivatives by oxidation (Scheme 13). Treatment of 2-*epi*-CJ-16,170 (**8.6**) with the Dess-Martin reagent gave the corresponding aldehyde **13.1** in almost quantitative yield (98%). Cladobotryal (**1**) was oxidized to the corresponding acid **13.2** in 76% yield, using the same conditions ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, MeCN/*t*-BuOH/H_2O) employed to make **7.13** (see Scheme 7). Both derivatives have been submitted to Crompton Co. for evaluation as fungicides, but the test results are not yet available.


HO
Ph
O
N
H
8.6
Dess-Martin reagent, CH2Cl2
98%
OHC
Ph
13.1
NaClO2, NaH2PO4,
2-methyl-2-butene,
MeCN/t-BuOH/water
76%
HO2C
1
13.2

Scheme 13

3 CONCLUSION

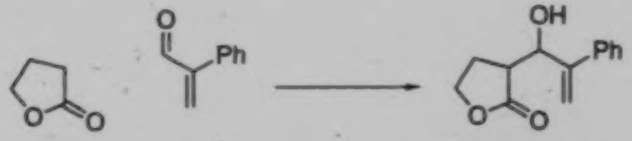
Our route to cladobotryal **1** provides the first method for making this natural product. The routes to 2-*epi*-CJ-16,170 (**8.6**) and to cladobotryal (**1**) should also work to generate analogs, at least simple ones in which the phenyl group is substituted, but we have not tried to do this. These approaches should also provide general methods of making 2- and 4-pyridinones, especially those that are not benzo-fused.

The above experiments illustrated an effective method for generating a quaternary carbon (**7.8** → **7.9**) with stereochemical control by an adjacent stereogenic center using radical cyclization. Aromatization (**8.3** → **8.5**) with DDQ in the presence of TsOH provided a method of dehydrogenation when other methods failed. Replacement of an *N*-Boc group by *N*-CO_2SiPr-i_3 (**11.4a** → **12.1a**, **11.4b** → **12.1b**), and related interconversions, may be generally useful where standard methods for Boc removal do not work, as found in the present synthesis. We expect that the method we have used to generate the second double bond of the pyridinone has general promise in cases where more traditional methods of dehydrogenation fail.

4 EXPERIMENTAL

General Procedures. The same general procedures were used as described in Chapter 1 of this Thesis. In many ^{1}H NMR spectra, certain spin systems are described as AB even though the value of $\Delta\nu/J$ is greater than 10. Strictly, such spectra should be described as AM systems.

Dihydro-3-(1-hydroxy-2-phenyl-2-propenyl)furan-2-one (5.2a,b).



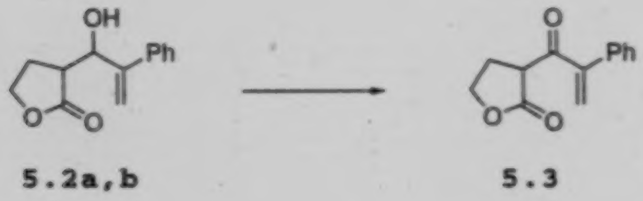
5.1 **4.3** **5.2a,b**

BuLi (2.5 M in hexanes, 4.0 mL, 10 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.4 mL, 10 mmol) in THF (20 mL). Stirring at 0 °C was continued for 15 min, and the solution was then cooled to -78 °C. A solution of **5.1** (0.75 mL, 0.98 mmol) in THF (12 mL) was then added dropwise. The mixture was stirred at -78 °C for 90 min and freshly-made aldehyde **4.3**[14] (435 mg, 3.28 mmol) in THF (12 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and saturated aqueous NH_4Cl (10 mL) was added, followed by EtOAc (100 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl and brine, and the organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 2:5 EtOAc-hexane, gave **5.2** as two diastereoisomers: diastereoisomer A (**5.2a**, less polar, 35 mg, 5%) was obtained as a liquid and diastereoisomer B (**5.2b**, more polar, 515 mg, 72%) as a solid.

Diastereoisomer A (**5.2a**) had: FTIR (CH_2Cl_2, cast) 3455, 3055, 2989, 2915, 1758, 1634, 1598, 1574; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.90 (dddd, *J* = 12.8, 9.6, 7.5, 3.3 Hz, 1 H), 2.34 (dq, *J* = 12.8, 9.6 Hz, 1 H), 2.39 (d, *J* = 4.0 Hz, 1 H), 2.64 (dt, *J* = 2.4, 9.6 Hz, 1 H), 4.11 (dt, *J* = 7.5, 8.9 Hz, 1 H), 4.33 (dt, *J* = 3.3, 8.9 Hz, 1 H); 5.34 (br s, 1 H), 5.39 (t, *J* = 1.3 Hz, 1 H), 5.51 (t, *J* = 1.5 Hz, 1 H), 7.27-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (t), 43.8 (d), 67.2 (t), 70.0 (d), 113.3 (t), 126.6 (d), 128.2 (d), 128.7 (d), 138.9 (s), 148.7 (s), 178.6 (s); exact mass *m/z* calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0947.

Diastereoisomer B (**5.2b**) had: mp 77-79 °C; FTIR (CH_2Cl_2, cast) 3477, 2988, 2914, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77-2.04 (m, 2 H), 2.67 (dt, *J* = 11.2, 9.0 Hz, 1 H), 4.06 (ddd, *J* = 10.2, 9.0, 6.7 Hz, 1 H), 4.27 (dt, *J* = 2.2, 8.9 Hz, 1 H), 4.39 (s, 1 H), 4.65 (d, *J* = 8.9 Hz, 1 H), 5.41 (d, *J* = 1.1 Hz, 1 H), 5.44 (s, 1 H), 7.25-7.37 (m, 3 H), 7.46-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.1 (t), 43.6 (d), 67.0 (t), 75.8 (d), 117.3 (t), 127.7 (d), 128.0 (d), 128.4 (d), 139.1 (s), 147.8 (s), 179.8 (s); exact mass *m/z* calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0947.

Dihydro-3-(1-oxo-2-phenyl-2-propenyl)furan-2-one (5.3).

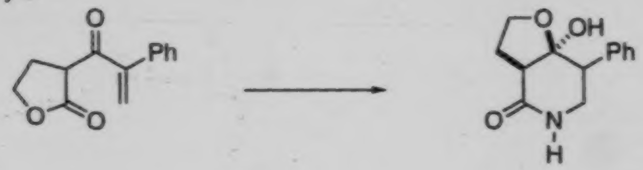


5.2a,b **5.3**

Dess-Martin reagent (444 mg, 1.05 mmol) was added in one portion to a stirred solution of **5.2a,b** (mixture of diastereoisomers) (0.176 g, 0.806 mmol) in CH_2Cl_2 (18 mL). The mixture was stirred for 1 h, diluted with Et_2O (50 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 20 cm), using CH_2Cl_2, gave **5.3** (125 mg, 72%) as an oil: FTIR (CH_2Cl_2, cast) 3057, 2991, 2917, 1767, 1682, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (dddd, J = 12.8, 9.2, 8.0, 6.3 Hz, 1 H), 2.72 (ddt, J = 12.8, 8.0, 6.3 Hz, 1 H), 4.27-4.36 (m, 2 H), 4.43 (ddd, J = 8.8, 8.0, 6.3 Hz, 1 H), 6.16 (s, 1 H), 6.35 (s, 1 H), 7.28-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.2 (t), 48.3 (d), 67.5 (t), 128.2 (d), 128.36 (d), 128.4 (d), 128.8 (s), 136.3 (s), 147.9 (t), 172.7 (s), 194.8 (s); exact mass *m/z* calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0782.

In earlier separate experiments, the individual diastereoisomers of **5.2a** and **5.2b** each gave **5.3**, under the above conditions, but in lower yield (ca 65%).

Hexahydro-7a-hydroxy-7-phenylfuro[3,2-*c*]pyridin-4-one (5.4).

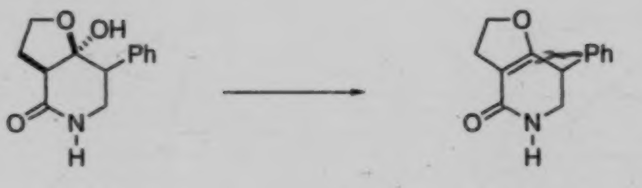


5.3 **5.4**

NH_4Cl (890 mg, 16.6 mmol) and concentrated (28-30% w/w) ammonia solution (13 mL) were added successively to a stirred solution of **5.3** (420 mg, 1.94 mmol) in MeOH (50 mL), and stirring was continued for 1 h. The mixture was then placed in a preheated oil bath set at 50 °C, and stirring was continued for 1 h. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:25 MeOH-CH_2Cl_2, gave **5.4** (200 mg, 44%) as an oil, which was a mixture of two diastereoisomers: FTIR (CH_2Cl_2, cast) 3304, 2891, 1660 cm^{-1}; the ^1H NMR spectrum was too complex to be of diagnostic value; ^{13}C NMR ($CDCl_3$, 50.3 MHz) (signals for both diastereoisomers) δ 28.8 (t), 29.2 (t), 42.4 (t), 43.7 (t), 48.5 (d), 50.3 (d), 51.2 (d), 51.5 (d), 66.7 (t), 67.3 (t), 103.5 (s), 104.4 (s), 128.0 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.0 (d), 129.9 (d), 135.2 (s), 135.7 (s), 173.2 (s), 173.5 (s); exact mass *m/z* calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1047.

3,5,6,7-Tetrahydro-7-phenyl-2*H*-furo[3,2-*c*]-

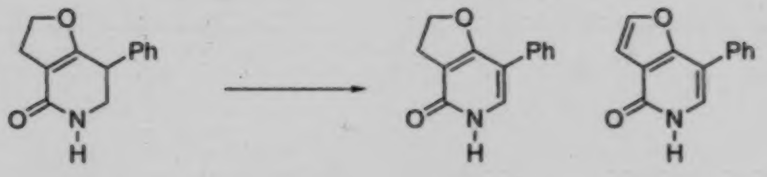
pyridin-4-one (5.5).



5.4 **5.5**

TsOH.H_2O (24.0 mg, 0.139 mmol) was added to a stirred solution of **5.4** (mixture of diastereoisomers) (65.0 mg, 0.279 mmol) in PhMe (30 mL) and the mixture was stirred at 115 °C (oil bath) for 5 h, cooled and evaporated. Flash chromatography the residue over silica gel (1.5 x 15 cm), using 1:30 MeOH-CH_2Cl_2, gave **5.5** (48 mg, 80%) as a white solid: mp 165-166 °C; FTIR ($CDCl_3$, cast) 3216, 3062, 2870, 1671, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.88-3.06 (m, 2 H), 3.45 (dd, J = 14.0, 8.8 Hz, 1 H), 3.73-3.81 (m, 2 H), 4.51-4.63 (m, 2 H), 5.62 (br s, 1 H), 7.21-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (t), 40.4 (d), 47.3 (t), 73.1 (t), 106.0 (s), 127.8 (d), 127.9 (d), 128.9 (d), 137.2 (s), 168.0 (s), 170.0 (s); exact mass m/z calcd for $C_{13}H_{13}NO_2$ 215.0946, found 215.0951.

3,5-Dihydro-7-phenyl-2*H*-furo[3,2-*c*]pyridin-4-one (5.6) and 7-Phenyl-5*H*-furo[3,2-*c*]pyridin-4-one (5.7).



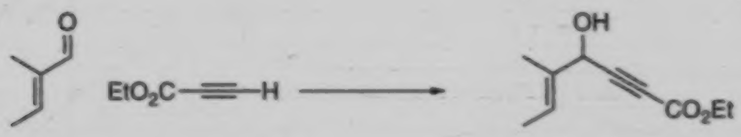
5.5 **5.6** **5.7**

DDQ (75.0 mg, 0.330 mmol) was added to a stirred solution of **5.5** (48.0 mg, 0.223 mmol) in PhH (40 mL). The mixture was lowered into a preheated oil bath set at 85 °C, stirred for 3 days, cooled to room temperature, and evaporated. The residue was dissolved in EtOAc (100 mL), and the solution was washed with 5% NaOH (20 mL) and brine (20 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL). All the organic extracts were combined, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 35 cm), using 1:30 to 1:10 MeOH-CH_2Cl_2, gave **5.6** (17 mg, 36%), **5.7** (25 mg, 53%) and starting material (**5.5**) (5 mg, 10%).

Compound **5.6** had: mp 242-244 °C; FTIR (CH_2Cl_2 cast) 2927, 2850, 1655, 1597, 1576, 1566, 1502 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.15 (t, J = 9.2 Hz, 2 H), 4.74 (t, J = 9.2 Hz, 2 H), 7.28-7.34 (m, 1 H), 7.36-7.43 (m, 2 H), 7.45 (s, 1 H), 7.49-7.54 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 27.0 (t), 73.6 (t), 109.8 (s), 111.1 (s), 127.7 (d), 127.9 (d), 128.9 (d), 133.7 (s), 134.3 (d), 163.1 (s), 167.8 (s); exact mass m/z calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0793. The structure was confirmed by single crystal X-ray analysis. Details of the analysis may be obtained from Dr. R. McDonald of the X-ray Crystallography Laboratory in this Department.

Compound **5.7** had: mp 195-197 °C; FTIR ($CDCl_3$, cast) 3106, 3050, 1665, 1598, 1556, 1523 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 2.1 Hz, 1 H), 7.33-7.50 (m, 3 H), 7.52 (s, 1 H), 7.62 (d, J = 2.1 Hz, 1 H), 7.64-7.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 106.9 (d), 112.2 (s), 116.1 (s), 127.5 (d), 127.9 (d), 128.3 (d), 128.9 (d), 132.5 (s), 143.8 (d), 158.9 (s), 161.6 (s); exact mass *m/z* calcd for $C_{13}H_9NO_2$ 211.0633, found 211.0635.

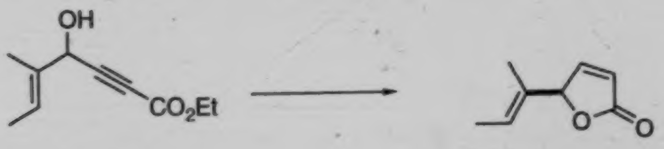
(*E*)-4-Hydroxy-5-methylhept-5-en-2-ynoic Acid Ethyl Ester (6.3).



6.2 **6.1** **6.3**

BuLi (2.5 M in hexanes, 8.30 mL, 20.7 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (2.90 mL, 20.7 mmol) in THF (40 mL). Stirring was continued at 0 °C for 15 min, and the solution was then cooled to -78 °C. A solution of **6.1** (2.0 mL, 19.7 mmol) in THF (20 mL) was added dropwise to the LDA solution. Stirring at -78 °C was continued for 1 h, and a solution of **6.2** (1.90 mL, 19.7 mmol) was added dropwise. Stirring at -78 °C was continued for 1 h, and saturated aqueous NH_4Cl (24 mL) was added. The cooling bath was removed, stirring was continued for 30 min, and water (100 mL) was added. The mixture was extracted with Et_2O (3 x 100 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:3 EtOAc-hexane, gave **6.3** (3.130 g, 87%) as a liquid: FTIR (CH_2Cl_2, cast) 3409, 2985, 2921, 2863, 2235, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, J = 7.1 Hz, 3 H), 1.66 (d, J = 6.7, 3 H), 1.77 (s, 3 H), 1.97 (br s, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 4.87 (s, 1 H), 5.74 (q, J = 6.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (q), 13.3 (q), 14.0 (q), 62.1 (t), 67.7 (d), 77.4 (s), 85.9 (s), 124.3 (d), 133.2 (s), 153.3 (s); exact mass m/z calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0940.

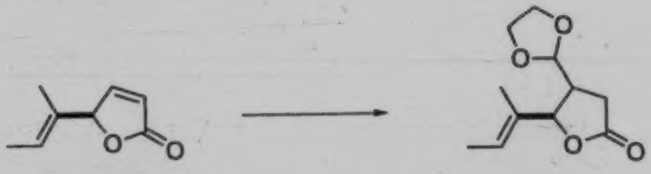
5-[(*E*)-1-Methylpropenyl]-5*H*-furan-2-one (6.4).



6.3 **6.4**

Aqueous KOH (5% w/v, 98 mL) was added dropwise to a stirred and cooled (0 °C) solution of **6.3** (5.240 g, 28.76 mmol) in EtOH (70 mL). Stirring was continued at 0 °C for 10 min. The ice bath was removed, stirring was continued for 50 min, and the EtOH was evaporated (water pump, rotary evaporator). Quinoline (0.90 mL, 7.6 mmol), water (250 mL) and $Pd/BaSO_4$ (5% w/w, 1.42 g, 0.667 mmol) were added successively to the aqueous solution. The black suspension was stirred under H_2 (1 atm) for 5 h (ca 640 mL H_2 absorbed). The catalyst was filtered off through a pad of Celite (4 x 3 cm), and the pad was washed with water (200 mL) and Et_2O (200 mL). The resulting mixture was extracted with Et_2O (2 x 200 mL) to remove neutral byproducts, and the aqueous phase was then acidified to pH 1 with cold 5% v/v aqueous HCl. The mixture was extracted with CH_2Cl_2 (4 x 150 mL), and the extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was kept at room temperature overnight. Flash chromatography over silica gel (2.5 x 30 cm), using 1:2 EtOAc-hexane, then gave **6.4** (2.784 g, 70%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2920, 1790, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 3 H), 1.68 (d, *J* = 6.7 Hz, 3 H), 5.36 (s, 1 H), 5.71 (q, *J* = 6.7 Hz, 1 H), 6.16 (dd, *J* = 5.7, 2.1 Hz, 1 H), 7.33 (dd, *J* = 5.7, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.4 (q), 13.3 (q), 88.3 (d), 121.9 (d), 126.6 (d), 129.7 (s), 155.4 (d), 173.1 (s); exact mass *m/z* calcd for $C_8H_{10}O_2$ 138.0681, found 138.0685.

Dihydro-4-(1,3-dioxolan-2-yl)-5-[(*E*)-1-methylpropenyl]furan-2-one (6.5).

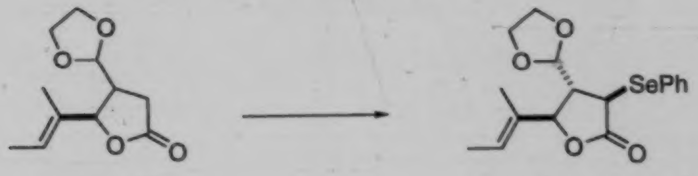


6.4

6.5

A solution of AIBN (6.0 mg, 0.037 mmol) and $(PhCO)_2O_2$ (9.0 mg, 0.037 mmol) in 1,3-dioxolane (2 mL) was added over 3 h (syringe pump) to a stirred and heated (oil bath at 80 °C) solution of **6.4** (100 mg, 0.724 mmol) in 1,3-dioxolane (3 mL). After an additional 7 h at 80 °C, the mixture was cooled to room temperature, evaporated and diluted with Et_2O (100 mL). The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 35 cm), using 1:3 EtOAc-hexane, gave **6.5** (97.0 mg, 63%) as a colorless oil, which was a single diastereoisomer: FTIR (CH_2Cl_2, cast) 2891, 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 3 H), 1.62 (d, J = 6.7 Hz, 3 H), 2.50-2.65 (m, 3 H), 3.81-4.03 (m, 4 H), 4.76 (d, J = 5.0 Hz, 1 H), 4.85 (d, J = 3.0 Hz, 1 H), 5.56 (q, J = 6.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.1 (q), 13.1 (q), 28.9 (t), 42.1 (d), 65.37 (t), 65.43 (t), 85.0 (d), 103.0 (d), 123.6 (d), 132.2 (s), 176.2 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{16}NaO_4$ 235.09463, found 235.09434.

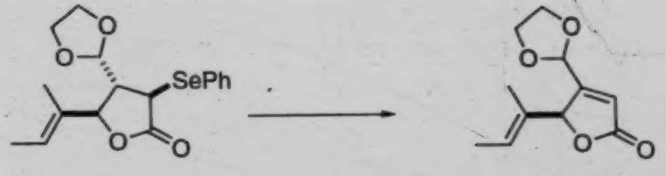
Dihydro-4-(1,3-dioxolan-2-yl)-5-[(*E*)-1-methylpropenyl]-3-(phenylselanyl)furan-2-one (6.6).



6.5 **6.6**

BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.70 mL, 5.0 mmol) in THF (40 mL). Stirring was continued at 0 °C for 15 min, and the solution was cooled to -78 °C. A solution of **6.5** (0.5150 g, 2.426 mmol) in THF (20 mL) was added dropwise to the LDA solution. Stirring at -78 °C was continued for 3 h, and a solution of PhSeCl (0.973 g, 5.08 mmol) in THF (20 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and saturated aqueous NH_4Cl (25 mL) was added. The cooling bath was removed, stirring was continued for 30 min, and water (50 mL) was added. The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 1:6 EtOAc-hexane, gave **6.5** (120 mg, 23%) and **6.6** (0.535 g, 60%, 78% corrected for recovered starting material) as a yellow oil: FTIR (CH_2Cl_2, cast) 2889, 1768, 1577 cm^{-1}; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.6 (q), 13.2 (q), 37.8 (d), 48.4 (d), 65.3 (t), 65.5 (t), 83.2 (d), 102.4 (d), 124.3 (d), 127.2 (s), 129.0 (d), 129.3 (d), 131.9 (s), 136.2 (d), 175.2 (s); exact mass (electrospray) *m/z* calcd for $C_{17}H_{20}NaO_4{}^{80}Se$ 391.0425, found 391.04165.

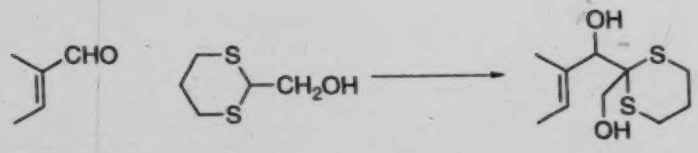
4-(1,3-Dioxolan-2-yl)-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (6.7).



6.6 **6.7**

Pyridine (0.54 mL, 6.7 mmol) and H_2O_2 (30%, 0.78 mL, 6.9 mmol) were added successively to a stirred solution of **6.6** (0.535 g, 1.46 mmol) in CH_2Cl_2 (50 mL). Stirring was continued at room temperature for 30 min, and the mixture was diluted with Et_2O (100 mL), washed successively with water, saturated aqueous $CuSO_4$, water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:3 EtOAc-hexane, gave **6.7** (0.247 g, 81%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2894, 1792, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3 H), 1.67 (d, J = 6.8 Hz, 3 H), 3.85-4.02 (m, 4 H), 5.33 (d, J = 1.5 Hz, 1 H), 5.47 (s, 1 H), 5.75 (q, J = 6.8 Hz, 1 H), 6,14 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.6 (q), 13.5 (q), 65.2 (t), 65.6 (t), 87.7 (d), 98.1 (d), 118.8 (d), 128.4 (d), 129.4 (s), 165.9 (s), 172.0 (s); exact mass *m/z* calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0893.

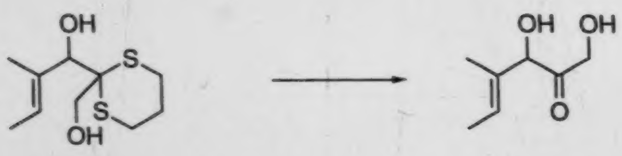
(*E*)-1-[2-Hydroxymethyl-1,3-dithian-2-yl]-2-methylbut-2-en-1-ol (7.2).



6.2 **7.1** **7.2**

BuLi (2.5 M in hexane, 30 mL, 75 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of alcohol **7.1** (5.10 g, 33.9 mmol) in THF (100 mL). Stirring was continued at -78 °C for 1 h, and (*E*)-2-methyl-2-butenal (3.86 mL, 40 mmol) was then added dropwise. Stirring at -78 °C was continued for 90 min and saturated aqueous NH_4Cl (50 mL) was added, followed by Et_2O (300 mL). The cooling bath was removed and, after 30 min, the mixture was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 3 cm), using 1:2 EtOAc-hexane, gave starting alcohol **7.1** (1.713 g, 34%), and **7.2** (4.441 g, 56%) as a solid: mp, 75-77 °C; FTIR (CH_2Cl_2, cast) 3406, 2915, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.63 (d of multiplets, $J = 6.7$ Hz, 3 H), 1.76 (t, $J = 1.2$ Hz, 3 H), 1.79-1.92 (m, 1 H), 1.96-2.08 (m, 1 H), 2.63 (dd, $J = 5.3$, 3.8 Hz, 1 H), 2.68 (dd, $J = 5.4$, 3.7 Hz, 1 H), 2.72 (br s, 2 H), 2.76-2.90 (m, 2 H), 3.87 (AB q, $J = 12.0$ Hz, $\Delta\nu_{AB} = 46.0$ Hz, 2 H), 4.27 (s, 1 H), 5.60 (q of multiplets, $J = 6.7$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.3 (q), 13.5 (q), 24.6 (t), 25.5 (t), 25.9 (t), 59.7 (s), 63.7 (t), 81.5 (d), 126.1 (d), 133.3 (s); exact mass m/z calcd for $C_{10}H_{18}O_2S_2$ 234.0748, found 234.0750.

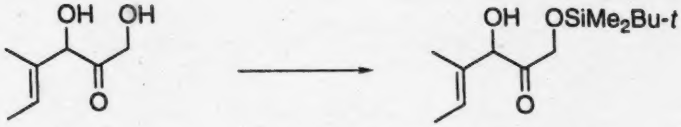
(*E*)-1,3-Dihydroxy-4-methylhex-4-en-2-one (7.3).



7.2 **7.3**

$PhI(OCOCF_3)_2$ (18.33 g, 42.62 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **7.2** (6.660 g, 28.42 mmol) in 9:1 MeOH-water (120 mL).[20] The ice bath was removed and stirring was continued for 15 min. Saturated aqueous $NaHCO_3$ (100 mL) was added, and the mixture was subjected to continuous extraction with Et_2O (300 mL) for 24 h. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:1 EtOAc-hexane, gave **7.3** (3.199 g, 78%) as an oil: FTIR (CH_2Cl_2, cast) 3387, 2918, 2862, 1727, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46-1.50 (m, 3 H), 1.66 (d of multiplets, J = 6.7 Hz, 3 H), 2.80 (br s, 1 H), 3.43 (br s, 1 H), 4.24-4.40 (m, 2 H), 4.58 (s, 1 H), 5.70 (q of multiplets, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.7 (q), 13.5 (q), 65.1 (t), 81.2 (d), 127.6 (d), 132.8 (s), 210.2 (s); exact mass m/z calcd for $C_7H_{12}O_3$ 144.0786, found 144.0787.

(*E*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-4-methylhex-4-en-2-one (7.4).

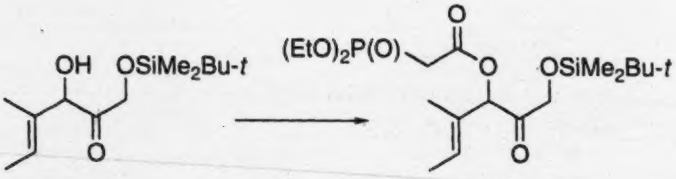


7.3 **7.4**

t-BuMe$_2$SiCl (1.7714 g, 11.752 mmol) and pyridine (2.3 mL, 28 mmol) were added successively to a stirred and cooled (0 °C) solution of **7.3** (1.540 g, 10.68 mmol) in DMF (28 mL). After 45 min at 0 °C, the pyridine was removed by evaporation (rotary evaporator, water pump, room temperature). The residue was diluted with Et$_2$O (350 mL), washed with brine (3 times), dried (Na$_2$SO$_4$) and evaporated. Flash chromatography the residue over silica gel (2 x 25 cm), using 1:10 EtOAc-hexane, gave **7.4** (2.282 g, 83%) as a colorless oil: FTIR (CH$_2$Cl$_2$ cast) 3483, 2954, 2929, 2886, 2858, 1733 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.47 (t, J = 1.1 Hz, 3 H), 1.65 (d of multiplets, J = 6.7 Hz, 3 H), 3.61 (d, J = 5.2 Hz, 1 H), 4.32 (s, 2 H), 4.69 (d, J = 5.0 Hz, 1 H), 5.68 (q of multiplets, J = 6.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) (two signals overlap in this spectrum) δ -5.4 (q), 11.0 (q), 13.7 (q), 18.4 (s), 25.8 (q), 66.5 (t), 80.3 (d), 127.0 (d), 132.9 (s), 209.3 (s); exact mass (electrospray) m/z calcd for C$_{13}$H$_{26}$NaO$_3$Si 281.1543, found 281.1539.

(Diethylphosphoryl)ethanoic Acid (*E*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-oxoethyl]-2-methyl-

but-2-enyl Ester (7.5).

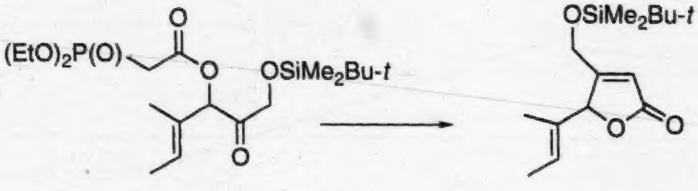


7.4 **7.5**

DCC (3.210 g, 0.0156 mol) was added in one portion to a stirred and cooled (0 °C) solution of **7.4** (3.660 g, 0.0142 mol) in CH_2Cl_2 (64 mL). Diethylphosphonoacetic acid (2.5 mL, 0.016 mol) was then added dropwise. After 90 min at 0 °C, the mixture was filtered and the solid was rinsed with CH_2Cl_2 (50 mL). The filtrate was dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (5 x 25 cm), using 1:1 EtOAc-hexane, gave **7.5** (5.810 g, 94%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2930, 2857, 1738, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6 H), 0.86 (s, 9 H), 1.29 (dt, J = 0.25, 7.1 Hz, 3 H), 1.30 (dq, J = 0.25, 7.1 Hz, 3 H), 1.60 (t, J = 1.2 Hz, 3 H), 1.63 (d of multiplets, J = 6.7 Hz, 3 H), 3.00 (d of AB q, J = 21.4, 14.5 Hz, $\Delta\nu_{AB}$ = 21.0 Hz, 2 H), 4.09-4.18 (m, 4 H), 4.32 (AB q, J = 18.0 Hz, $\Delta\nu_{AB}$ = 14.1 Hz, 2 H), 5.60 (s, 1 H), 5.70 (q of multiplets, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.5 (q), -5.4 (q), 12.3 (q), 13.7 (q), 16.36 [q(d, $^3J_{PC}$ = 6.1 Hz)], 16.38 [q(d, $^3J_{PC}$ = 6.1 Hz)], 18.5 (s), 25.8 (q), 34.0 [t(d, $^1J_{PC}$ = 133.5 Hz)], 62.7 [t(d, $^2J_{PC}$ = 6.5 Hz)], 62.8 [t(d, $^2J_{PC}$ = 6.5 Hz)], 67.3 (t), 82.0 (d), 128.6 (s), 128.9 (d), 164.9 [s(d, $^2J_{PC}$ = 6.1

Hz)], 202.9 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{38}O_7PSi$ 437.2119, found 437.2117.

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (7.6).

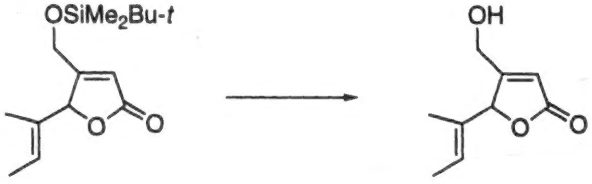


7.5 **7.6**

LiBr (2.13 g, 24.5 mmol), followed by Et_3N (11.5 mL, 82.5 mmol), were added to a stirred and cooled (0 °C) solution of **7.5** (3.565 g, 8.166 mmol) in dry THF (200 mL) (Ar atmosphere).[21] Stirring at 0 °C was continued for 30 min. The cooling bath was removed and stirring was continued for 5 h. The mixture was filtered through a pad of silica gel (4 x 3 cm), using Et_2O (200 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 1:10 EtOAc-hexane, gave **7.6** (1.650 g, 72%) as a solid: mp 46-47 °C; FTIR (CH_2Cl_2, cast) 2955, 2929, 2858, 1790, 1759, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.39-1.41 (m, 3H) 1.67 (d of multiplets, *J* = 6.7 Hz, 3 H), 4.24 [(apparent AB q, *J* = 17.3 Hz, $\Delta\nu_{AB}$ = 31.1 Hz (each component of the apparent AB q is split by long-range coupling), 2 H], 5.19 (s, 1 H), 5.68 (q of multiplets, *J* = 6.7 Hz, 1 H), 6.04-6.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6

MHz) (two signals overlap in this spectrum) δ -5.4 (q), 9.4 (q), 13.6 (q), 18.3 (s), 25.8 (q), 59.4 (t), 87.6 (d), 116.2 (d), 128.1 (d), 130.0 (s), 170.8 (s), 172.5 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{27}O_3Si$ 283.1724, found 283.1721.

4-(Hydroxymethyl)-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (7.7).

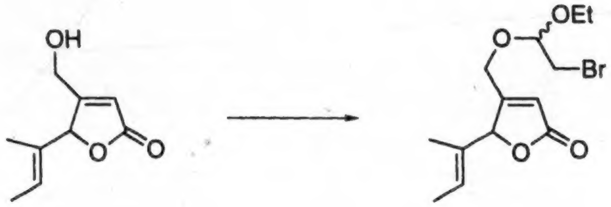


7.6 **7.7**

TsOH.H_2O (72.0 mg, 0.418 mmol) was added to a stirred solution of **7.6** (0.5330 g, 1.887 mmol) in MeOH (88 mL). Stirring was continued for 15 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:1 EtOAc-hexane, gave **7.7** (0.310 g, 98%) as an oil: FTIR (CH_2Cl_2, cast) 3426, 2919, 2862, 1791, 1747, 1673, 1645; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3 H), 1.64 (dd, *J* = 6.7, 0.9 Hz, 3 H), 2.78 (br s, 1 H), 4.26 [apparent AB q, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 23.5 Hz (each component of the apparent AB q is split by long-range coupling), 2 H], 5.19 (s, 1 H), 5.68 (q of multiplets, *J* = 6.7 Hz, 1 H), 6.06 (q, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.2 (q), 13.5 (q), 58.7 (t), 88.0 (d), 115.9 (d), 128.5 (d), 129.7 (s), 171.5 (s), 173.2 (s);

exact mass *m/z* calcd for $C_9H_{12}O_3$ 168.0786, found 168.0785.

4-[(2-Bromo-1-ethoxyethoxy)methyl]-5-[(*E*)-1-methylpropenyl]-5*H*-furan-2-one (7.8).

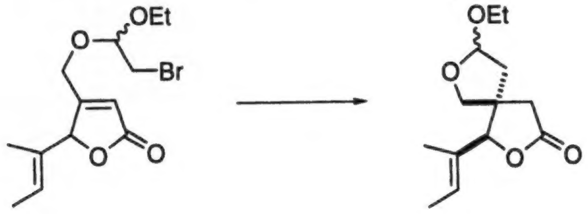


7.7 **7.8**

Br_2 (0.83 mL, 16 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ethyl vinyl ether (1.9 mL, 20 mmol) in CH_2Cl_2. After 15 min at -78 °C, the cooling bath was removed and stirring was continued for 15 min. The mixture was recooled to -78 °C and a solution of **7.7** (1.09 g, 6.48 mmol) and 2,6-lutidine (2.3 mL, 20 mmol) in CH_2Cl_2 was added dropwise. Stirring was continued for 1 h at -78 °C after the addition, the cooling bath was removed, and stirring was continued for 2 h. Water (20 mL) was added to the mixture, which was then diluted with Et_2O (400 mL), washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 8 cm), using 1:7 EtOAc-hexane, gave **7.8** (1.95 g, 94%) as an oil, which was a mixture of two diastereoisomers: FTIR (CH_2Cl_2, cast) 2977, 2919, 1790, 1757, 1652 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.90 (t, J = 7.1 Hz, 3 H), 1.12-1.16 (m, 3 H), 1.24-

1.30 (m, 3 H), 2.94 (d, J = 5.6 Hz, 1 H), 2.95 (d, J = 5.5 Hz, 1 H), 3.00-3.22 (m, 2 H), 3.59-3.78 (m, 2 H), 4.31 (t, J = 5.6 Hz, 0.5 H), 4.32 (t, J = 5.5 Hz, 0.5 H), 4.74-4.79 (m, 1 H), 5.19-5.28 (m, 1 H), 5.96-5.99 (m, 1H); ^{13}C NMR (C_6D_6, 100.6 MHz) (some of the signals overlap; the spectrum is too complicated to identify the signals of the individual diastereoisomers) δ 9.09 (q), 9.11 (q), 13.2 (q), 15.1 (q), 30.88 (t), 30.93 (t), 60.5 (t), 61.2 (t), 62.35 (t), 62.41 (t), 87.2 (d), 87.3 (d), 101.1 (d), 101.6 (d), 117.7 (d), 117.9 (d), 127.6 (d), 130.6 (s), 130.7 (s), 166.2 (s), 166.4 (s), 171.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{20}{}^{79}BrO_4$ 319.0545, found 319.0541.

(1*R,5*S**)-8-Ethoxy-1-[(*E*)-1-methylpropenyl]-2,7-dioxaspiro[4.4]nonan-3-one (7.9a,b).**



7.8 **7.9a,b**

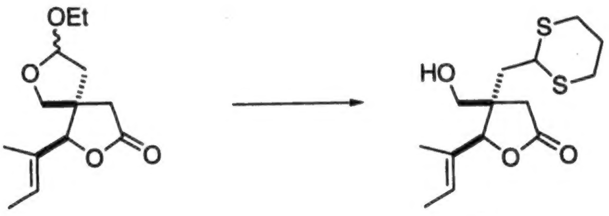
A solution of Bu_3SnH (4.4 mL, 16 mmol) and AIBN (170.0 mg, 1.035 mmol) in PhH (50 mL) was added over 3 h to a stirred and heated (oil bath at 80 °C) solution of **7.8** (1.950 g, 6.109 mmol) and AIBN (30.0 mg, 0.183 mmol) in PhH (80 mL). The mixture was refluxed for 2 h after the addition, cooled to room temperature, and evaporated. Et_2O (100 mL), followed by aqueous KF (10%, 80 mL) was added and the mixture was stirred overnight (ca 15 h). The mixture was filtered through a pad of Celite (4 x 3 cm), using Et_2O (200 mL). The filtrate was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 1:5 to 1:4 EtOAc-hexane, gave **7.9a** (less polar) (0.688 g, 48%) as a colorless oil and **7.9b** (more polar) (0.656 g, 45%) as a solid.

Compound **7.9a** had: FTIR (CH_2Cl_2 cast) 2976, 2929, 1781 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.1 Hz, 3 H), 1.56-1.59 (m, 3 H), 1.65 (d of multiplets, J = 6.7 Hz, 3 H), 2.00 (dd, J = 13.3, 1.5 Hz, 1 H), 2.21 (dd, J = 13.3, 5.4 Hz, 1 H), 2.75 (AB q, J = 18.0 Hz, $\Delta\nu_{AB}$ = 39.6 Hz, 2 H), 3.39 (dq, J = 9.6, 7.1 Hz, 1 H), 3.68 (dq, J = 9.6, 7.1 Hz, 1 H), 3.74 (AB q, J = 9.1 Hz, $\Delta\nu_{AB}$ = 26.8 Hz, 2 H), 4.67 (s, 1 H), 5.11 (dd, J = 5.4, 1.5 Hz, 1 H), 5.57 (q of quintets, J = 6.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.6 (q), 13.1 (q), 15.2 (q), 41.0 (t), 45.5 (t), 49.5 (s), 63.0 (t), 72.1 (t), 91.6 (d), 103.3 (d), 125.6 (d), 130.6 (s), 175.4 (s); exact mass m/z calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1359.

Compound **7.9b** had: mp 75-77 °C; FTIR (CH_2Cl_2, cast) 2975, 2927, 1781 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, J = 7.1 Hz, 3 H), 1.57 (t, J = 1.1 Hz, 3 H), 1.65 (d of multiplets, J = 6.8 Hz, 3 H), 2.05 (dd, J = 13.3, 5.2 Hz, 1 H), 2.14 (dd, J = 13.3, 2.8 Hz, 1 H), 2.56 (AB q, J = 7.7 Hz, $\Delta\nu_{AB}$ = 98.9 Hz, 2 H), 3.40 (dq, J = 9.5, 7.1 Hz, 1 H), 3.68

(AB q, J = 8.9 Hz, $\Delta\nu_{AB}$ = 46.6 Hz, 2 H), 3.69 (dq, J = 9.5, 7.1 Hz, 1 H), 4.98 (s 1 H), 5.14 (dd, J = 5.2, 2.8 Hz, 1 H), 5.58 (q of multiplets, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.5 (q), 13.3 (q), 15.2 (q), 41.1 (t), 46.3 (t), 49.7 (s), 63.3 (t), 71.3 (t), 90.9 (d), 103.4 (d), 126.0 (d), 130.5 (s), 175.1 (s); exact mass m/z calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1359. The structure was determined by single crystal X-ray analysis. Details of the analysis may be obtained from Dr. R. McDonald of the X-ray Crystallography Laboratory in this Department.

(4*R**,5*S**)-4-[(1,3-Dithian-2-yl)methyl]-4-(hydroxymethyl)-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (7.10).

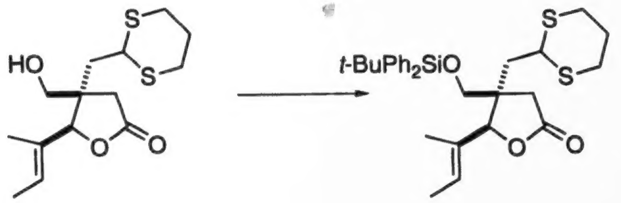


7.9a,b **7.10**

TiCl$_4$ (1.2 mL, 11 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **7.9a,b** (a mixture diastereoisomers, 1.312 g, 5.460 mmol) and 1,3-propanedithiol (1.65 mL, 16.4 mmol) in CH_2Cl_2 (120 mL). The cold bath was left in place but was not recharged, and stirring was continued for 3 h, by which time the temperature had risen to

-20 °C. Saturated aqueous $NaHCO_3$ (100 mL) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was diluted with EtOAc (100 mL) and filtered through a pad of Celite (4 x 3 cm), using EtOAc (400 mL). The filtrate was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 1:2 EtOAc-hexane, gave **7.10** (1.360 g, 82%) as a colorless, thick oil: FTIR (CH_2Cl_2, cast) 3465, 2904, 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d of multiplets, *J* = 6.7 Hz, 3 H), 1.68-1.70 (m, 3 H), 1.78-2.15 (m, 5 H), 2.64 (AB q, *J* = 17.6 Hz, $\Delta\nu_{AB}$ = 17.8 Hz, 2 H), 2.82 (ddd, *J* = 14.3, 4.6, 3.3 Hz, 2 H), 2.88-2.98 (m, 2 H), 3.56 (AB q, *J* = 11.8 Hz, $\Delta\nu_{AB}$ = 30.8 Hz, 2 H), 4.07 (t, *J* = 5.8 Hz, 1 H), 4.62 (s, 1 H), 5.69 (q of multiplets, *J* = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 13.2 (q), 13.8 (q), 25.0 (t), 31.0 (t), 38.0 (t), 41.5 (t), 43.0 (d), 48.5 (s), 63.8 (t), 89.5 (d), 124.2 (d), 130.3 (s), 175.2 (s); exact mass *m/z* calcd for $C_{14}H_{22}O_3S_2$ 302.1010, found 302.1011.

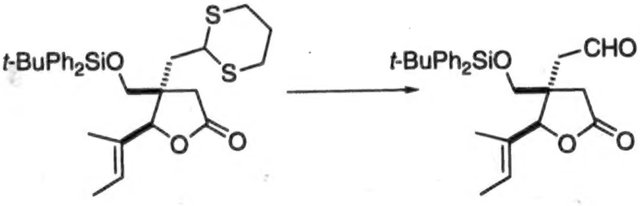
(4*R**,5*R**)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-4-[(1,3-dithian-2-yl)methyl]-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (7.11).



7.10 **7.11**

Imidazole (1.530 g, 22.47 mmol) was added in one portion to a stirred solution of **7.10** (1.360 g, 4.497 mmol) in CH_2Cl_2 (100 mL), and t-$BuPh_2SiCl$ (5.8 mL, 22 mmol) was then added dropwise. The mixture was stirred for 24 h, saturated aqueous NH_4Cl solution (120 mL) was added, and the mixture was extracted with Et_2O (200 mL). The organic extract was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (3 x 25 cm), using 1:8 EtOAc-hexane, gave **7.11** (2.160 g, 89%) as a colorless, thick oil: FTIR (CH_2Cl_2, cast) 3070, 2930, 2857, 1779, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.49 (t, J = 1.0 Hz, 3 H), 1.55 (d of multiplets, J = 6.7 Hz, 3 H), 1.71-1.83 (m, 1 H), 1.80 (dd, J = 15.1, 6.9 Hz, 1 H), 1.99-2.08 (m, 1 H), 2.04 (dd, J = 15.1, 5.2 Hz, 1 H), 2.66 (AB q, J = 17.6 Hz, $\Delta\nu_{AB}$ = 25.5 Hz, 2 H), 2.67-2.84 (m, 4 H), 3.46 (AB q, J = 10.6 Hz, $\Delta\nu_{AB}$ = 26.9 Hz, 2 H), 3.93 (dd, J = 6.9, 5.2 Hz, 1 H), 4.67 (s, 1 H), 5.56 (q of multiplets, J = 6.7 Hz, 1 H), 7.34-7.46 (m, 6 H), 7.57-7.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (three signals overlap in this spectrum) δ 13.1 (q), 13.4 (q), 19.2 (s), 25.1 (t), 26.9 (q), 30.9 (t), 31.0 (t), 38.0 (t), 41.0 (t), 43.1 (d), 48.5 (s), 65.2 (t), 89.7 (d), 124.5 (d), 127.77 (d), 127.83 (d), 129.6 (s), 129.9 (d), 130.0 (d), 132.6 (s), 132.8 (s), 135.79 (d), 135.82 (d), 175.5 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{41}O_3S_2Si$ 541.2261, found 541.2262.

(2*R,3*S**)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-[(*E*)-1-methylpropenyl]-5-oxotetrahydrofuran-3-yl]ethanal (7.12).**

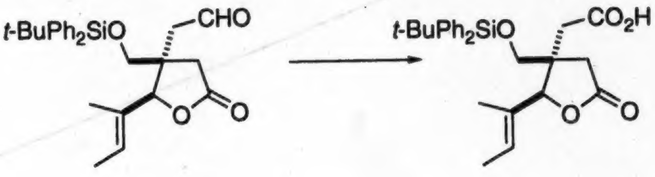


7.11 **7.12**

HgO (2.17 g, 10.0 mmol) and $HgCl_2$ (2.72 g, 10.0 mmol) were added successively to a stirred solution of **7.11** (2.16 g, 3.99 mmol) in 10:1 acetone-water (66 mL). The mixture was stirred at 55 °C (oil bath) for 40 h, cooled to room temperature and filtered through a pad of Celite (4 x 3 cm), using Et_2O (250 mL). The filtrate was washed with aqueous KI (10%) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:6 EtOAc-hexane, gave starting **7.11** (210 mg, 9.7%) and **7.12** (1.550 g, 86% or 95% after correction for recovered **7.11**) as a colorless oil: FTIR (CH_2Cl_2, cast) 3071, 2930, 2857, 2029, 1958, 1782, 1722, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.43 (s, 3 H), 1.53 (d, J = 6.8 Hz, 3

H), 2.62 (dd, J = 16.9, 1.4 Hz, 1 H), δ 2.65 (AB q, J = 17.6 Hz, $\Delta\nu_{AB}$ = 40.6 Hz, 2 H), 2.79 (dd, J = 16.9, 2.1 Hz, 1 H), 3.50 (AB q, J = 10.4 Hz, $\Delta\nu_{AB}$ = 44.6 Hz, 2 H), 4.70 (s, 1 H), 5.50 (q of multiplets, J = 6.8 Hz, 1 H), 7.35-7.48 (m, 6 H), 7.53-7.59 (m, 4 H), 9.73 (dd, J = 2.1, 1.4 Hz, 1H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 13.0 (q), 13.1 (q), 19.2 (s), 26.9 (q), 37.8 (t), 47.3 (s), 48.6 (t), 65.3 (t), 89.4 (d), 125.0 (d), 127.8 (d), 127.9 (d), 129.3 (s), 130.0 (d), 130.1 (d), 132.3 (s), 132.5 (s), 135.57 (d), 135.62 (d), 175.0 (s), 199.4 (d); exact mass (electrospray) m/z calcd for $C_{27}H_{34}NaO_4Si$ 473.2119, found 473.2121.

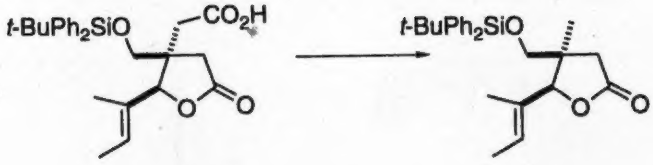
(2*R,3*S**)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-[(*E*)-1-methylpropenyl]-5-oxotetrahydrofuran-3-yl]ethanoic acid (7.13).**



7.12 **7.13**

A solution of $NaClO_2$ (3.05 g, 33.7 mmol) and NaH_2PO_4 (3.86 g, 28.0 mmol) in water (20 mL) was added over 5 min to a stirred and cooled (0 °C) solution of **7.12** (1.500 g, 3.329 mmol) in 4:4:1 MeCN-t-BuOH-2-methyl-2-butene (75 mL). The mixture was stirred for an additional 20 min at 0 °C, and then extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum (0.025 mmHg) for 5 h, and then diluted with EtOAc (ca 20 mL). The solvent was evaporated and the residue was kept under oil pump vacuum for 2 h, to afford the crude acid **7.13** (1.770 g, ca 100%). An analytical sample was recrystallized from EtOAc-hexane: mp 153-154 °C; FTIR (CH_2Cl_2, cast) 3071, 2931, 2858, 1781, 1752, 1709, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.43 (s, 3 H), 1.52 (d, J = 6.8 Hz, 3 H), 2.64 (AB q, J = 15.9 Hz, $\Delta\nu_{AB}$ = 74.7 Hz, 2 H), 2.70 (AB q, J = 17.8 Hz, $\Delta\nu_{AB}$ = 33.1 Hz, 2 H), 3.48 (AB q, J = 10.4 Hz, $\Delta\nu_{AB}$ = 32.7, 2 H), 4.80 (s, 1 H), 5.52 (q of multiplets, J = 6.8 Hz, 1 H), 7.33-7.45 (m, 6 H), 7.54-7.59 (m, 4 H), [the CO_2H signal was not detected (0-17 ppm)]; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.06 (q), 13.13 (q), 19.2 (s), 26.9 (q), 37.6 (t), 38.1 (t), 47.1 (s), 65.4 (t), 88.5 (d), 124.8 (d), 127.79 (d), 127.84 (d), 129.3 (s), 129.97 (d), 130.04 (d), 132.4 (s), 132.6 (s), 135.6 (d), 135.7 (d), 175.26 (s), 175.33 (s); exact mass (electrospray) m/z calcd for $C_{27}H_{34}NaO_5Si$ 489.2068, found 489.2067. Anal. Calcd for $C_{27}H_{34}O_5Si$: C 69.49; H 7.34. Found: C 69.19; H 7.48.

(4*R,5*S**)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-4-methyl-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (7.14).**

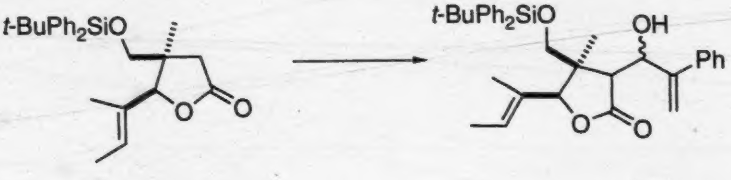


7.13 **7.14**

A solution of crude acid **7.13** (1.770 g, crude, ca 3.319 mmol), Et_3N (1.90 mL, 13.6 mmol) and DMAP (41.0 mg, 0.336 mmol) in THF (32 mL) was added dropwise with stirring to an aluminum foil-wrapped flask containing HOTT[25] (2.00 g, 5.38 mmol). The mixture was stirred in the dark for 2 h. *t*-Dodecanethiol (1.60 mL, 6.79 mmol) was then added to the resulting bright yellow solution of the Barton ester and the aluminum foil was removed. The mixture was refluxed (oil bath 75 °C) for 1 h, cooled and diluted with Et_2O (200 mL). The mixture was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (2 x 30 cm), using 1:8 EtOAc-hexane, gave **7.14** (1.074 g, 76% over two steps) as a solid: mp 83-85 °C; FTIR ($CDCl_3$, cast) 2963, 2858, 1783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.21 (s, 3 H), 1.50-1.53 (m, 3 H), 1.56 (d of multiplets, J = 6.8 Hz, 3 H), 2.47 (AB q, J = 17.3 Hz, $\Delta\nu_{AB}$ = 152.3 Hz, 2 H), 3.38 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 45.4 Hz, 2 H), 4.53 (s, 1 H), 5.56 (q of multiplets, J = 6.8 Hz, 1 H), 7.35-7.47 (m, 6 H), 7.57-7.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 13.0 (q), 13.3 (q), 19.2 (s), 22.9 (q), 26.8 (q), 40.0 (t), 45.4 (s), 66.7 (t), 91.5 (d), 123.6 (d), 127.71 (d), 127.73

(d), 129.6 (s), 129.81 (d), 129.83 (d), 132.9 (s), 133.0 (s), 135.6 (d), 175.8 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{34}NaO_3Si$ 445.2170, found 445.2163.

(4*R,5*S**)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-(1-hydroxy-2-phenyl-2-propenyl)-4-methyl-5-[(*E*)-1-methylpropenyl]dihydrofuran-2-one (8.1a,b).**



7.14 **8.1a,b**

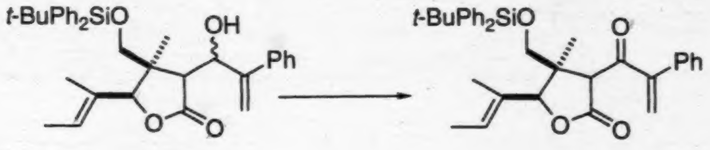
A solution of **7.14** (550 mg, 1.30 mmol) in THF (12 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (2.60 mmol) in THF (10 mL). The mixture was stirred at -78 °C for 30 min, the cold bath was replaced by an ice bath, and stirring was continued for 45 min. The mixture was recooled to -78 °C and freshly-made aldehyde **4.3**[14] (305 mg, 2.31 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at -78 °C for 3.5 h, and saturated aqueous NH_4Cl (10 mL) was added, followed by Et_2O (150 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 40 cm), using 1:6 EtOAc-hexane, gave **8.1** as two diastereoisomers: **8.1a** (less polar, 0.370 g, 51%) as a solid and **8.1b** (more polar, 270 mg) as a thick oil, which was not pure. **8.1b** was crystallized from Et_2O-hexane to afford the pure compound (144 mg, 20%) as a white solid.

8.1a had: mp 140-141 °C; FTIR (CH_2Cl_2, cast) 3451, 3051, 2931, 2858, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9 H), 1.33 (s, 3 H), 1.35 (t, J = 1.1 Hz, 3 H), 1.45 (d of multiplets, J = 6.8 Hz, 3 H), 2.77 (d, J = 4.3 Hz, 1 H), 2.84 (d, J = 4.3 Hz, 1 H), 3.19 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 123.7 Hz, 2 H), 4.66 (s, 1 H), 5.25 (tt, J = 4.3, 1.5 Hz, 1 H), 5.31 (t, J = 1.2 Hz, 1 H), 5.46 (q of multiplets, J = 6.8 Hz, 1 H), 5.48 (t, J = 1.5 Hz, 1 H), 7.21-7.57 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.0 (q), 13.1 (q), 18.6 (q), 19.1 (s), 26.8 (q), 48.4 (s), 49.7 (d), 67.9 (t), 72.6 (d), 91.8 (d), 115.3 (t), 124.8 (d), 127.0 (d), 127.6 (d), 127.7 (d), 127.8 (d), 128.5 (d), 129.7 (d), 129.8 (d), 130.0 (s), 132.6 (s), 132.8 (s), 135.66 (d), 135.72 (d), 139.0 (s), 148.4 (s), 177.4 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{42}NaO_4Si$ 577.2745, found 577.2748.

8.1b had: mp 147-148 °C; FTIR (CH_2Cl_2, cast) 3452, 3051, 2930, 2858, 1752, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 9 H), 1.28 (s, 3 H), 1.41 (s, 3 H), 1.49 (d, J = 6.8 Hz, 3 H), 2.79 (d, J = 3.8 Hz, 1 H), 3.10 (d, J = 3.4 Hz, 1 H), 3.16 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 109.4 Hz, 2 H), 4.76 (s, 1 H), 4.92 (t, J = 3.6 Hz, 1 H), 5.34-5.38 (m, 2 H), 5.52 (q of multiplets, J = 6.8 Hz, 1 H), 7.18-7.49 (m, 15H); ^{13}C NMR

($CDCl_3$, 100.6 MHz) (two signals overlap in this spectrum) δ 12.9 (q), 13.3 (q), 17.4 (q), 19.0 (s), 26.7 (q), 47.5 (s), 49.3 (d), 67.1 (t), 72.4 (d), 90.8 (d), 115.2 (t), 124.1 (d), 127.2 (d), 127.56 (d), 127.62 (d), 127.7 (d), 128.5 (d), 129.4 (s), 129.65 (d), 129.71 (d), 132.8 (s), 132.9 (s), 135.6 (d), 139.2 (s), 148.5 (s), 175.9 (s); exact mass (electrospray) *m/z* calcd for $C_{35}H_{42}NaO_4Si$ 577.2745, found 577.2740.

(4*R,5*S**)-4-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-4-methyl-5-[(*E*)-1-methylpropenyl]-3-(1-oxo-2-phenyl-2-propenyl)dihydrofuran-2-one (8.2).**



8.1a **8.2**

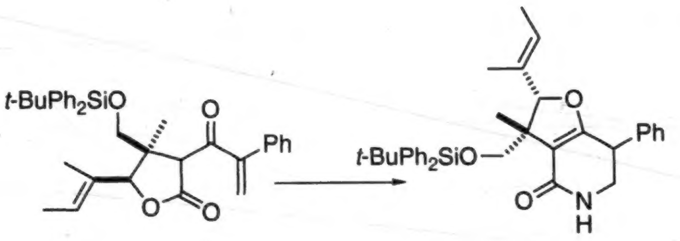
Dess-Martin reagent (558.0 mg, 1.316 mmol) was added in one portion to a stirred solution of **8.1a** (major diastereoisomer, 365 mg, 0.658 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 30 min, diluted with Et_2O (100 mL), washed with 2:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 30 cm), using 1:9 EtOAc-hexane, gave **8.2** (301 mg, 83%) as an oil: FTIR (CH_2Cl_2, cast) 3070, 2931, 2858, 1776, 1683, 1589 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) (signals for major component; minor signals were present, and we attribute these to an enolized form) δ 1.07 (two overlapping singlets, 12 H), 1.51 (s, 3 H), 1.56 (d of multiplets, J = 6.8 Hz, 3 H), 3.40 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 106.2, 2 H), 4.61 (s, 1 H), 4.89 (s 1 H), 5.56 (q of multiplets, J = 6.8 Hz, 1 H), 6.07 (s, 1 H), 6.11 (s, 1 H), 7.14-7.64 (m, 15H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (signals for major component; minor signals were present, and we attribute these to the enolized form) δ 13.0 (q), 13.5 (q), 17.3 (q), 19.2 (s), 26.8 (q), 49.8 (s), 56.6 (d), 67.5 (t), 89.8 (d), 124.0 (d), 127.82 (d), 127.84 (d), 128.0 (s), 128.3 (d), 128.46 (s), 128.52 (d), 128.55 (d), 129.96 (d), 130.01 (d), 135.6 (d), 135.7 (d), 135.8 (s), 149.9 (t), 172.8 (s), 197.2 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{40}NaO_4Si$ 575.2588, found 575.2585.

Oxidation of the minor diastereoisomer was more efficient with PCC than with the Dess-Martin reagent: Powdered 4 Å molecular sieves (50 mg) was added to a stirred solution of alcohol **8.1b** (minor diastereoisomer) (11.0 mg, 0.020 mmol) in dry CH_2Cl_2 (1 mL). PCC (8.5 mg, 0.04 mmol) was added and stirring was continued. After 1 h, another portion of PCC (4.5 mg, 0.02 mmol) was added and stirring was continued for 1.5 h. The mixture was diluted with Et_2O (5 mL) and the mixture was filtered through a pad (2 x 1.5 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 15 cm), using 1:9

EtOAc-hexane, gave ketone **8.2** (7.1 mg, 65%) as an oil, spectroscopically identical to material obtained from the major diastereoisomer.

(2*R,3*S**)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5,6,7-tetrahydro-2*H*-furo[3,2-*c*]pyridin-4-one (8.4a,b).**



8.2 **8.4a,b**

TsOH.H_2O (20.0 mg, 0.116 mmol) and powdered 4 Å molecular sieves (800 mg) were added successively to a stirred solution of crude **8.3** [prepared, as described below, from **8.2** (110 mg, 0.199 mmol)] in PhMe (20 mL), and the mixture was stirred at 110 °C (oil bath) for 15 h. The mixture was cooled and filtered through a pad (3 x 2 cm) of Grade III neutral alumina, using EtOAc (80 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 40 cm), using 2:3 EtOAc-hexane, gave **8.4** as two individual diastereoisomers, each of which contained small impurities: diastereoisomer A (**8.4a**, less polar, 29.0 mg, 26%) as a solid and diastereoisomer B (**8.4b**, more polar, 20.5 mg, 19%) as a thick oil.

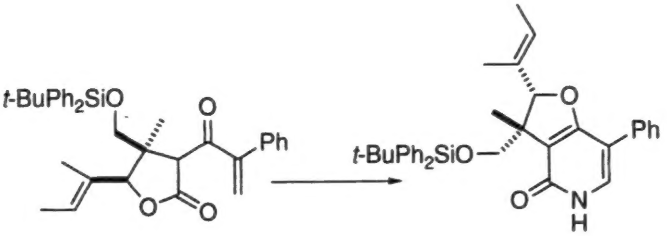
Diastereoisomer A (**8.4a**) had: mp 175-178 °C; FTIR (CH_2Cl_2 cast) 3203, 3069, 1780, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9 H), 1.50 (s, 3 H), 1.54 (d of multiplets, J = 6.8 Hz, 3 H), 1.62 (t, J = 0.9 Hz, 3 H), 3.36 (ddd, J = 12.1, 5.8, 2.9 Hz, 1 H), 3.70 (ddd, J = 12.1, 6.3, 1.7 Hz, 1 H), 3.74 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 3.4 Hz, 2 H), 3.77 (t, J = 6.1 Hz, 1 H), 4.65 (s, 1 H), 5.01 (s, 1 H), 5.59 (q of multiplets, J = 6.8 Hz, 1 H), 7.24-7.65 (m, 15H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.1 (q), 14.0 (q), 19.4 (s), 23.1 (q), 27.1 (q), 40.4 (d), 47.5 (t), 51.2 (s), 64.7 (t), 98.2 (d), 110.3 (s), 122.6 (d), 127.38 (d), 127.4 (d), 127.6 (d), 127.7 (d), 128.7 (d), 129.37 (d), 129.43 (d), 130.7 (s), 133.4 (s), 133.6 (s), 135.7 (d, two overlapping signals), 137.7 (s), 167.0 (s), 168.6 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{42}NO_3Si$ 552.2934, found 552.2934.

A sample was recrystallized from EtOAc-hexane for X-ray analysis. Details of the analysis may be obtained from Dr. R. McDonald of the X-ray Crystallography Laboratory in this Department.

Diastereoisomer B (**8.4b**) had: FTIR (CH_2Cl_2 cast) 3228, 3070, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.52 (s, 3 H), 1.53 (d, J = 6.8 Hz, 3 H), 1.58 (br s, 3 H), 3.38 (ddd, J = 12.1, 7.2, 2.3 Hz, 1 H), 3.67 (ddd, J = 12.1, 6.4, 2.1 Hz, 1 H), 3.79 (t, J = 6.8 Hz, 1 H), 3.81 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 66.1 Hz, 2 H), 4.69 (s, 1 H), 4.98 (br s, 1 H), 5.45 (q of multiplets, J = 6.8 Hz, 1 H), 7.21-7.67 (m, 15H);

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.1 (q), 14.0 (q), 19.3 (s), 23.4 (q), 27.0 (q), 40.8 (d), 47.5 (t), 51.2 (s), 64.6 (t), 98.2 (d), 111.2 (s), 122.5 (d), 127.4 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.7 (d), 129.4 (d), 129.5 (d), 131.4 (s), 133.4 (s), 133.8 (s), 135.8 (d), 135.9 (d), 137.3 (s), 167.1 (s), 168.5 (s); exact mass (electrospray) *m/z* calcd for $C_{35}H_{42}NO_3Si$ 552.2934, found 552.2925.

(2*R,3*S**)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5-dihydro-2*H*-furo[3,2-*c*]pyridin-4-one (8.5).**



8.2 **8.5**

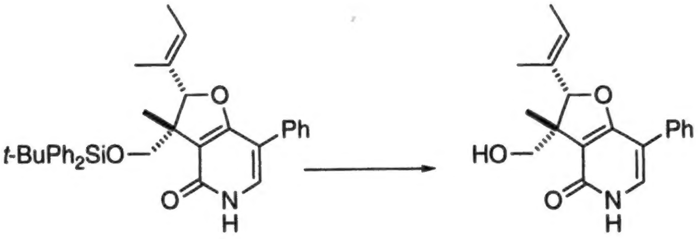
NH_4Cl (115 mg, 2.15 mmol) and concentrated (880) ammonia solution (1.9 mL)[26] were added successively to a stirred solution of **8.2** (120 mg, 0.217 mmol) in MeOH (10 mL), and the mixture was stirred for 2 h. The mixture was then placed in an oil bath set at 40 °C, and stirring was continued for 20 h. The mixture was cooled to room temperature and evaporated. The residue was diluted with 1:2 CH_2Cl_2-EtOAc (30 mL). The solution was dried ($MgSO_4$), and filtered through a pad of silica gel (2 x 3 cm), using EtOAc (3 x 30 mL).

Evaporation of the filtrate gave the crude product (**8.3**) (123 mg).

TsOH.H_2O (22.0 mg, 0.128 mmol) and DDQ (102 mg, 0.449 mmol) were added to a stirred solution of the above crude product (123 mg) in PhMe (20 mL) and the mixture was stirred at 110 °C (oil bath) for 2 h. The mixture was cooled and evaporated. The residue was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (30 mL), and the all the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1 x 40 cm), using 3:2 EtOAc-hexane, gave **8.5** (60.0 mg, 50%) as a yellow solid: mp 205-207 °C; FTIR (CH_2Cl_2, cast) 3047, 2930, 2857, 1654, 1622, 1600, 1578, 1561 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (s, 9 H), 1.58 (s, 3 H), 1.66 (d, J = 6.7 Hz, 3 H), 1.76 (s, 3 H), 3.82 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 6.9 Hz, 2 H), 4.87 (s, 1 H), 5.77 (q of multiplets, J = 6.7 Hz, 1 H), 7.22-7.64 (m, 16 H; it was not clear if the NH signal is in this multiplet); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.2 (q), 14.2 (q), 19.2 (s), 21.3 (q), 26.8 (q), 50.6 (s), 64.4 (t), 97.7 (d), 111.0 (s), 113.6 (s), 122.4 (d), 127.3 (d), 127.45 (d), 127.46 (d), 127.6 (d), 128.6 (d), 129.40 (d), 129.43 (d), 130.5 (s), 133.27 (s), 133.32 (s), 133.6 (s), 134.6 (d), 135.7 (d), 135.8 (d), 162.4 (s), 166.6 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{40}NO_3Si$ 550.2772, found 550.2763.

In an earlier experiment, omission of DDQ gave **8.4a,b** as a mixture of two diastereoisomers, as described above.

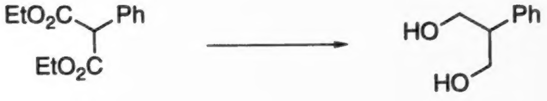
(2*R,3*S**)-3-(Hydroxymethyl)-3-methyl-2-[(*E*)-1-methylpropenyl]-7-phenyl-3,5-dihydro-2*H*-furo[3,2-*c*]pyridin-4-one (8.6).**



8.5 **8.6**

Bu_4NF (1 M in THF, 0.45 mL, 0.45 mmol) was added dropwise to a stirred solution of **8.5** (50.0 mg, 0.091 mmol) in THF (10 mL). Stirring was continued for 90 min, and then saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with EtOAc (3 x 6 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (0.8 x 25 cm), using 1:40 MeOH-CH_2Cl_2 (containing ca six drops of Et_3N), gave (±)-**8.6** (24.0 mg, 85%) as a pale yellow solid: mp 194-195 °C; FTIR (CD_2Cl_2, cast) 2925, 2862, 1648, 1614, 1598, 1559, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 3 H), 1.57 (s, 3 H), 1.63 (d, J = 6.8 Hz, 3 H), 3.64 (AB q, J = 10.9 Hz, $\Delta\nu_{AB}$ = 167.1 Hz, 2 H), 4.0-4.8 (br signal, not integrated), 4.93 (s, 1 H), 5.55 (q, J = 6.8 Hz, 1 H), 7.29-7.34 (m, 1 H), 7.36-7.42 (m, 2 H), 7.49 (s, 1 H), 7.50-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) (two signals overlap in this spectrum) δ 13.2 (two overlapping quartets), 24.6 (q), 49.4 (s), 66.5 (t), 99.5 (d), 111.9 (s), 116.8 (s), 124.9 (d), 127.5 (d), 127.7 (d), 128.7 (d), 131.2 (s), 132.4 (s), 134.5 (d), 162.9 (s), 166.8 (s); exact mass *m/z* calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1525.

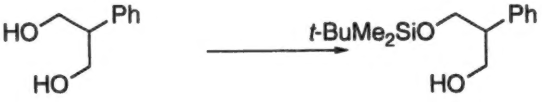
2-Phenylpropane-1,3-diol (9.2).[32]



9.1 **9.2**

Diethyl phenylmalonate **9.1** (0.800 g, 3.39 mmol) in Et_2O (7 mL) was added dropwise to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (0.2570 g, 6.772 mmol) in dry Et_2O (15 mL). The cooling bath was removed and stirring was continued for 10 h. The mixture was recooled to 0 °C and 3:1 MeOH-H_2O (4 mL) was added dropwise. The ice bath was removed and stirring was continued for 1 h. The mixture was diluted with Et_2O (100 mL), filtered through a Celite pad (2 x 3 cm), washed with brine (10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 20 cm), using 4:1 EtOAc-hexane, gave **9.2** (0.340 g, 66%) as a white solid: mp 50.5-51.5 °C; FTIR (CH_2Cl_2, cast) 3328, 3061, 3026, 2935, 2884, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.60 (s, 2 H), 3.04 (tt, J = 7.6, 5.5 Hz, 1 H), 3.88 (dd, J = 10.8, 5.5 Hz, 2 H), 3.94 (dd, J = 10.8, 7.6 Hz, 2 H), 7.17-7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.7 (d), 65.9 (t), 127.1 (d), 127.9 (d), 128.7 (d), 139.2 (s); exact mass *m/z* calcd for $C_9H_{12}O_2$ 152.0837, found 152.0839.

3-[(*tert*-Butyldimethylsilanyl)oxy]-2-phenylpropan-1-ol (9.3).[32]

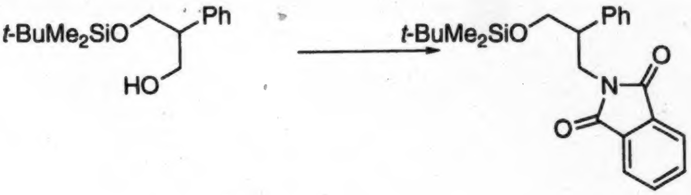


9.2 **9.3**

A solution of 2-phenylpropane-1,3-diol **9.2** (1.000 g, 6.571 mmol) in THF (5 mL) was added dropwise to a stirred and cooled (ice-bath) suspension of NaH (60% suspension in oil, 289 mg, 7.22 mmol) in THF (3 mL). The ice-bath was removed and stirring was continued for 1 h. The mixture was recooled to 0 °C and a solution of *t*-$BuMe_2SiCl$ (1.089 g, 7.225 mmol) in THF (6 mL) was added dropwise. The ice bath was removed and stirring was continued for 10 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (100 mL). The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:20 EtOAc-hexane, gave **9.3** (1.550 g, 88%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3406, 3063, 3029, 2954, 2928, 2884, 2857, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 2.60 (br s, 1 H), 3.02-3.11 (m, 1 H), 3.87 (dd, J = 10.8, 5.2 Hz, 1 H), 3.91 (d, J = 7.0 Hz, 2 H), 4.05 (dd, J = 10.8, 7.6 Hz, 1 H), 7.17-7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.61 (q), -5.57

(q), 18.2 (s), 25.8 (q), 49.6 (d), 66.7 (t), 67.4 (t), 127.0 (d), 128.0 (d), 128.6 (d), 139.7 (s); exact mass *m/z* (M + H) calcd for $C_{15}H_{27}O_2Si$ 267.1780, found 267.1773.

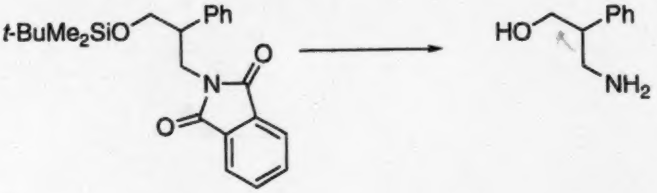
2-[3-[(*tert*-Butyldimethylsilanyl)oxy]-2-phenylpropyl]isoindole-1,3-dione (9.4).



9.3 **9.4**

Ph_3P (5.600 g, 21.35 mmol) and phthalimide (2.520 g, 17.13 mmol) were added successively to a stirred and cooled (0 °C) solution of alcohol **9.3** (3.800 g, 14.26 mmol) in THF (60 mL). DEAD (3.00 g, 17.2 mmol) in THF (15 mL) was then added dropwise. The cold bath was left in place and stirring was continued for 5 h. The mixture was diluted with Et_2O (300 mL), washed successively with saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:15 to 1:10 EtOAc-hexane, gave **9.4** (5.148 g, 91%) as a white solid: mp 67-68 °C; FTIR (CH_2Cl_2, cast) 3030, 2953, 2928, 2885, 2856, 1774, 1716, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -0.11 (s, 6 H), 0.79 (s, 9 H), 3.39-3.50 (m, 1 H), 3.76-3.87 (m, 2 H), 4.01 (dd, J_{AB} = 13.7 Hz, J_{AX} = 8.1 Hz, 1 H), 4.04 (dd, J_{AB} = 13.7 Hz, J_{BX} = 7.7 Hz, 1 H), 7.08-7.28 (m, 5 H), 7.52-7.61 (m, 2 H), 7.66-7.74 (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ -5.81 (q), -5.79 (q), 18.1 (s), 25.6 (q), 40.5 (t), 46.3 (d), 66.2 (t), 122.8 (d), 126.9 (d), 128.10 (d), 128.14 (d), 131.9 (s), 133.5 (d), 139.5 (s), 168.0 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{29}NNaO_3Si$ 418.1809, found 418.1803.

3-Amino-2-phenylpropan-1-ol (9.9).

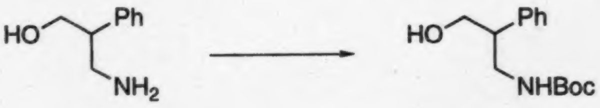


9.4 **9.9**

$NH_2NH_2.H_2O$ (16.0 mL, 0.333 mol) was added to a stirred solution of **9.4** (13.086 g, 33.079 mmol) in EtOH (500 mL) contained in a flask fitted with a reflux condenser. After 15 min, the mixture was lowered into a preheated oil bath set at 80 °C and stirring at this temperature was continued for 2 h. The mixture was cooled to room temperature and evaporated. The residue was diluted with Et_2O (600 mL) and washed with saturated aqueous $NaHCO_3$ (ca 200 mL). The aqueous layer was extracted with Et_2O (200 mL) and the combined organic phases were extracted with 5% hydrochloric acid (2 x 200 mL). The combined acidic aqueous extracts were treated with 10 N NaOH until pH >11, and then extracted with EtOAc (5 x 150 mL). The combined organic extracts were dried

($MgSO_4$) and evaporated, to give crude **9.9**[30,31] (4.63 g, 93%) as a colorless oil, which was used without further purification. Flash chromatography of a portion of the crude material over silica gel, using 1:2 MeOH-CH_2Cl_2, gave a pure sample: FTIR (CH_2Cl_2, cast) 3285, 3059, 3026, 2870, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (s, 3 H), 2.81-2.92 (m, 1 H), 3.01-3.14 (m, 2 H), 3.81 (dd, J_{AB} = 10.8 Hz, J_{AX} = 5.2 Hz, 1 H), 3.86 (dd, J_{AB} = 10.8 Hz, J_{BX} = 7.9 Hz, 1 H), 7.13-7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 46.1 (t), 49.9 (d), 67.4 (t), 126.8 (d), 127.8 (d), 128.6 (d), 140.7 (s); exact mass m/z calcd for $C_9H_{13}NO$ 151.0997, found 151.0999.

(3-Hydroxy-2-phenylpropyl)carbamic Acid *tert*-Butyl Ester (9.7).

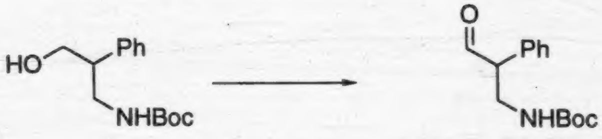


9.9 **9.7**

Acetone-water (4:1, 100 mL) was added to a stirred mixture of $NaHCO_3$ (3.50 g, 41.7 mmol) and **9.9** (1.000 g, 6.613 mmol). Boc_2O (1.580 g, 7.239 mmol) was added in one portion and stirring was continued for 4 h. The solvent was evaporated and the residue was diluted with Et_2O (250 mL), washed with water (ca 30 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 2:3 EtOAc-hexane, gave **9.7**[30]

(1.600 g, 96%) as a white solid: mp 58-59 °C; FTIR (CH_2Cl_2, cast) 3357, 3062, 3028, 2977, 2932, 1690, 1603, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (s, 9 H), 2.80 (br s, 1 H), 2.89 (quintet, J = 6.1 Hz, 1 H), 3.43-3.50 (m, 2 H), 3.78 (d, J = 6.1 Hz, 2 H), 4.69 (br s, 1 H), 7.18-7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 28.4 (q), 42.3 (t), 48.4 (d), 63.5 (t), 79.8 (s), 126.9 (d), 127.9 (d), 128.6 (d), 140.5 (s), 156.9 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{21}NNaO_3$ 274.1419, found 274.1419.

(3-Oxo-2-phenylpropyl)carbamic Acid *tert*-Butyl Ester (9.8).

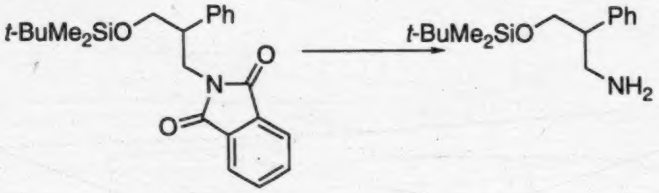


9.7 **9.8**

Dess-Martin reagent (4.85 g, 11.4 mmol) was added in one portion to a stirred solution of **9.7** (1.927 g, 7.667 mmol) in CH_2Cl_2 (100 mL). After 1 h, the mixture was diluted with Et_2O (200 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 EtOAc-hexane, gave aldehyde **9.8**[30] (1.781 g, 93%) as a white solid: mp 47-49 °C; FTIR (CD_2Cl_2, cast) 3358, 3030, 2977, 2933, 2720, 1717, 1601, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9 H), 3.41-3.52 (m, 1 H), 3.64 (ddd, J =

14.1, 8.1, 6.0 Hz, 1 H), 3.82-3.91 (m, 1 H), 4.86 (br s, 1 H), 7.15 (d, J = 7.3 Hz, 2 H), 7.27-7.39 (m, 3 H), 9.70 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 28.3 (q), 40.9 (t), 59.1 (d), 79.5 (s), 128.1 (d), 129.0 (d), 129.3 (d), 133.6 (s), 155.7 (s), 200.0 (d); exact mass (electrospray) m/z calcd for $C_{14}H_{19}NNaO$ 272.1263, found 272.1259.

3-[(*tert*-Butyldimethylsilanyl)oxy]-2-phenyl-propylamine (9.5).

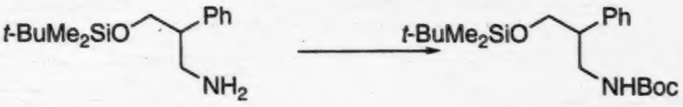


9.4 **9.5**

$NH_2NH_2.H_2O$ (0.35 mL, 7.2 mmol) was added dropwise to a stirred solution of **9.4** (0.277 g, 0.700 mmol) in EtOH (10 mL) contained in a flask fitted with a reflux condenser. After 10 min at room temperature, the mixture was lowered into a preheated oil bath set at 80 °C and stirring at this temperature was continued for 2 h. The mixture was cooled to room temperature and evaporated. The residue was diluted with Et_2O (40 mL) and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated to give **9.5** (180 mg, 97%) as a colorless oil, which was used without further purification. Flash chromatography of a portion of the crude material over silica gel, using 1:10 MeOH-hexane, gave a pure sample: FTIR

(CH_2Cl_2, cast) 3062, 3028, 2954, 2928, 2885, 2856, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -0.032 (s, 3 H), -0.027 (s, 3 H), 0.85 (s, 9 H), 1.20 (s, 2 H), 2.75-2.86 (m, 1 H), 3.04 (dd, J_{AB} = 12.6 Hz, J_{AX} = 8.3 Hz, 1 H), 3.06 (dd, J_{AB} = 12.6 Hz, J_{BX} = 5.4 Hz, 1 H), 3.73 (dd, J_{AB} = 10.0 Hz, J_{AX} = 7.2 Hz, 1 H), 3.75 (dd, J_{AB} = 10.0 Hz, J_{BX} = 5.6 Hz, 1 H), 7.16-7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.6 (q), -5.5 (q), 18.2 (s), 25.9 (q), 44.5 (t), 52.0 (d), 66.2 (t), 126.7 (d), 128.2 (d), 128.4 (d), 141.2 (s); exact mass *m/z* calcd for $C_{15}H_{27}NOSi$ 265.1862, found 265.1862.

[3-[(*tert*-Butyldimethylsilanyl)oxy]-2-phenylpropyl]carbamic Acid *tert*-Butyl Ester (9.6).

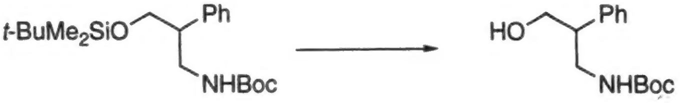


9.5 **9.6**

Acetone-water (4:1, 15 mL) was added to a stirred mixture of $NaHCO_3$ (530 mg, 6.31 mmol) and **9.5** (168 mg, 0.633 mmol). Boc_2O (170 mg, 0.779 mmol) was added in one portion and stirring was continued for 12 h. The solvent was evaporated and the residue was diluted with Et_2O (50 mL), washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 40 cm), using 1:15 EtOAc-hexane, gave **9.6** (231 mg, 100%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3359, 3063, 3030, 2955,

2929, 2896, 2857, 1812, 1758, 1716, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.02 (s, 6 H), 0.86 (s, 9 H), 1.39 (s, 9 H), 2.87-3.00 (m, 1 H), 3.35-3.49 (m, 1 H), 3.56 (ddd, J = 13.1, 7.2, 5.7 Hz, 1 H), 3.75 (dd, J_{AB} = 10.1 Hz, J_{AX} = 7.3 Hz, 1 H), 3.78 (dd, J_{AB} = 10.1 Hz, J_{BX} = 5.2 Hz, 1 H), 4.91 (br s, 1 H), 7.15-7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.6 (q), 18.2 (s), 25.8 (q), 28.4 (q), 43.8 (t), 47.8 (d), 67.0 (t), 78.9 (s), 126.9 (d), 128.0 (d), 128.5 (d), 140.4 (s), 155.9 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{35}NNaO_3Si$ 388.2284, found 388.2283.

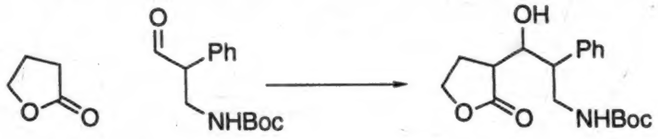
(3-Hydroxy-2-phenylpropyl)carbamic Acid *tert*-Butyl Ester (9.7).



9.6 **9.7**

Bu_4NF (1.0 M in THF, 0.13 mL, 0.13 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **9.6** (43.1 mg, 0.118 mmol) in THF (5 mL). After 10 min at 0 °C, the mixture was diluted with Et_2O (40 mL) and washed successively with water, saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1 x 25 cm), using 2:3 EtOAc-hexane, gave **9.7** (22 mg, 74%), which had spectral data corresponding to the material made previously.

[3-Hydroxy-3-(tetrahydro-2-oxofuran-3-yl)-2-phenylpropyl]carbamic Acid *tert*-Butyl Ester (10.1).

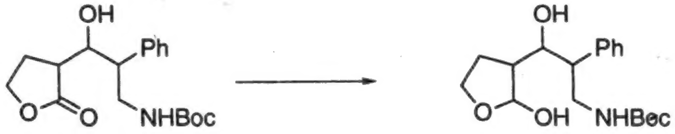


5.1 **9.8** **10.1**

BuLi (2.5 M in hexanes, 0.60 mL, 1.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.21 mL, 1.5 mmol) in THF (8 mL). Stirring at 0 °C was continued for 15 min, and the solution was then cooled to -78 °C. A solution of **5.1** (129 mg, 1.50 mmol) in THF (6 mL) was then added dropwise to the LDA solution. The mixture was stirred at -78 °C for 90 min, and a solution of **9.8** (188 mg, 0.754 mmol) and HMPA (0.26 mL, 1.5 mmol) in THF (4 mL) was added dropwise. Stirring at -78 °C was continued for 80 min, and saturated aqueous NH_4Cl (10 mL) was then added, followed by Et_2O (60 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl (twice) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 40 cm), using 1:3 to 1:1 EtOAc-hexane, gave starting aldehyde **9.8** (50.0 mg, 27%) and **10.1** (176 mg, 70%) as a mixture of diastereoisomers. A sample, obtained by recrystallization from EtOAc-hexane, contained one major diastereoisomer and a small amount of another diastereoisomer (^1H NMR and ^{13}C NMR): mp 145-147 °C; FTIR (CH_2Cl_2, cast)

3400, 2978, 2933, 1766, 1685, 1602, 1511 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 1.44 (s, 9 H), 2.11-2.25 (m, 2 H), 2.36-2.47 (m, 1 H), 3.22-3.46 (m, 2 H), 3.68-3.83 (m, 1 H), 3.95-4.01 (m, 1 H), 4.09 (q, *J* = 8.0 Hz, 1 H), 4.32 (dt, *J* = 5.3, 8.3 Hz, 1 H), 4.84 (br s, 2 H), 7.24-7.37 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 27.6 (t), 28.4 (q), 41.9 (d), 43.0 (t), 49.2 (d), 67.6 (t), 73.7 (d), 80.2 (s), 127.4 (d), 129.0 (d), 129.1 (d), 141.3 (s), 157.9 (s), 178.2 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{25}NNaO_5$ 358.1630, found 358.1628.

[3-Hydroxy-3-(tetrahydro-2-hydroxyfuran-3-yl)-2-phenylpropyl]carbamic Acid *tert*-Butyl Ester (10.2).

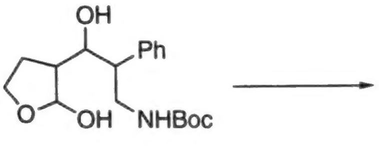


10.1 **10.2**

DIBAL-H (1 M in PhMe, 18 mL, 18 mmol) was added dropwise to a stirred and cooled solution (-78 °C) of **10.1** (2.000 g, 5.963 mmol) in CH_2Cl_2 (80 mL). Stirring at -78 °C was continued for 40 min, and 3:1 MeOH-water (15 mL) was added dropwise. The cooling bath was removed and stirring was continued for 1 h. The mixture was filtered through a pad of Celite (6 x 2 cm), using EtOAc (250 mL) as a rinse, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum overnight to afford crude **10.2**

(2.00 g, 99%), which was a mixture of diastereoisomers and was used without further purification: exact mass (electrospray) *m/z* calcd for $C_{18}H_{27}NNaO_5$ 360.1781, found 360.1784.

Hexahydro-4-hydroxy-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (10.3a,b,c).



10.2 **10.3a,b,c**

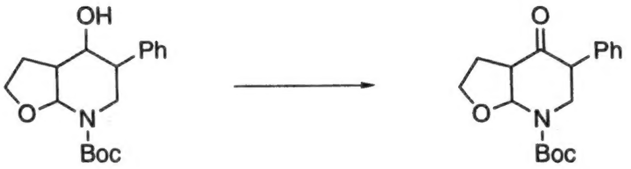
TsOH.pyridine (0.5450 g, 2.169 mmol) was added in one portion to a stirred solution of **10.2** (1.465 g, 4.342 mmol) in THF (90 mL). Stirring was continued for 1 h, and the mixture was diluted with Et_2O (150 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography the residue over silica gel (2 x 20 cm), using 1:2 to 1:1 EtOAc-hexane, gave **10.3a**,**b**,**c** as two fractions: fraction A (**10.3a**, less polar, 0.500 g, 36%) was obtained as a white solid, which was a single diastereoisomer (NMR), and fraction B (**10.3b**,**c**, more polar, 0.650 g, 47%) was obtained as a thick oil composed of two diastereoisomers (NMR), neither of which was the same as that in fraction A.

Fraction A (**10.3a**) had: mp 144-147 °C; FTIR (CH_2Cl_2, cast) 3454, 2976, 2932, 2886, 1699 cm^{-1}; ^1H NMR (CD_2Cl_2, 500

MHz) δ 1.46 (s, 9 H), 2.07 (br s, 1 H), 2.13-2.24 (m, 2 H), 2.27-2.33 (m, 1 H), 2.83 (ddd, J = 12.6, 4.1, 1.6 Hz, 1 H), 3.40-3.64 (m, 1 H), 3.72-4.06 (m, 4 H), 5.44-5.66 (m, 1 H), 7.23-7.37 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 27.4 (t), 28.4 (q), 37.9 (t), 40.6 (d), 45.9 (d), 65.2 (t), 71.2 (d), 80.9 (s), 83.7 (d), 127.2 (d), 128.4 (d), 128.8 (d), 141.5 (s), 155.3 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{25}NNaO_4$ 342.1676, found 342.1675.

Fraction B (**10.3b**,**c**) (two diastereoisomers, one major) had: FTIR (CH_2Cl_2, cast) 3436, 2976, 2932, 2883, 1701 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 1.45 (s, 9 H), 1.61 (d, J = 7.6 Hz, 1 H), 1.97-2.06 (m, 1 H), 2.08-2.20 (m, 2 H), 3.17 (q, J = 4.6 Hz, 1 H), 3.44 (dd, J = 13.2, 4.6 Hz, 1 H), 3.74-3.83 (m, 2 H), 3.95-4.02 (m, 1 H), 4.12 (dd, J = 13.2, 5.0 Hz, 1 H), 5.76 (d, J = 5.4 Hz, 1 H), 7.23-7.38 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 28.4 (q), 28.8 (t), 41.1 (d), 43.08 (t), 43.12 (d), 64.5 (t), 71.1 (d), 80.8 (s), 85.0 (d), 127.4 (d), 128.8 (d), 129.6 (d), 139.7 (s), 155.4 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{25}NNaO_4$ 342.1676, found 342.1678.

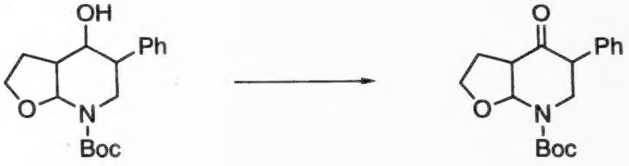
Hexahydro-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (10.4a).



10.3a **10.4a**

Dess-Martin reagent (258 mg, 0.608 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **10.3a** (fraction A) (0.150 g, 0.470 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 1 h, and the mixture was diluted with Et_2O (100 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 x 25 cm), using 1:3 EtOAc-hexane, gave **10.4a** (118 mg, 79%) as a white solid: mp 129-130 °C; FTIR (CD_2Cl_2, cast) 2977, 1702, 1572 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.50 (s, 9 H), 1.99-2.11 (m, 1 H), 2.64 (dddd, J = 12.6, 7.6, 4.6, 2.8 Hz, 1 H), 2.98 (ddd, J = 8.3, 5.5, 2.8 Hz, 1 H), 3.57 (br s, 1 H), 3.77 (dd, J = 12.2, 5.5 Hz, 1 H), 3.81 (dt, J = 4.6, 8.6 Hz, 1 H), 3.89 (q, J = 7.9 Hz, 1 H), 4.35 (br s, 1 H), 6.09 (br s, 1 H), 7.11-7.17 (m, 2 H), 7.27-7.40 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.1 (t), 28.4 (q), 45.3 (t, observed from 1D spectrum), 49.6 (d), 55.8 (d), 65.6 (t), 81.5 (s), 87.1 (d), 127.8 (d), 128.7 (d), 129.2 (d), 136.1 (s), 154.3 (s), 206.4 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{23}NNaO_4$ 340.1519, found 340.1515.

Hexahydro-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (10.4b).

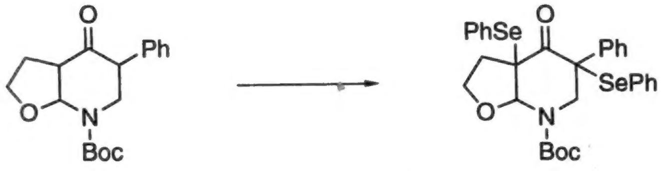


10.3b,c **10.4b**

Dess-Martin reagent (172 mg, 0.406 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **10.3b,c** (fraction B) (100 mg, 0.313 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h, and the mixture was diluted with Et_2O (100 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:3 EtOAc-hexane, gave **10.4b** (81 mg, 82%) as a colorless, thick oil: FTIR (CH_2Cl_2, cast) 3061, 2977, 2933, 2884, 1704, 1601 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.46 (s, 9 H), 2.01-2.12 (m, 1 H), 2.54 (dddd, J = 12.8, 7.9, 4.8, 3.1 Hz, 1 H), 2.93 (ddd, J = 8.6, 5.8, 3.1 Hz, 1 H), 3.72-3.81 (m, 3 H), 3.89 (q, J = 7.8 Hz, 1 H), 4.53 (d, J = 12.0 Hz, 1 H), 5.93 (d, J = 4.8 Hz, 1 H), 7.23-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 26.7 (t), 28.3 (q), 43.1 (t, observed in 1D spectrum), 47.7 (d), 53.5 (d), 65.4 (t), 81.5 (s), 86.5 (d), 127.7 (d), 128.0 (d), 129.2 (d), 136.8 (s), 154.7 (s), 207.6 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{23}NNaO_4$ 340.1519, found 340.1520.

Hexahydro-4-oxo-5-phenyl-3a,5-bis(phenylselanyl)-

furo[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (10.5).

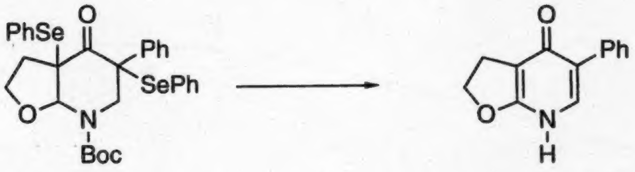


10.4a,b **10.5**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.430 mL, 0.215 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketones **10.4a,b** (65.0 mg, 0.205 mmol) in THF (4 mL). After 10 min, the cold bath was replaced by an ice bath and stirring was continued for 15 min. The mixture was recooled to -78 °C and a solution of PhSeCl (41.0 mg, 0.214 mmol) in THF (2 mL) was injected dropwise. After 15 min at -78 °C, the mixture was transferred to an ice bath and stirring was continued for 15 min. The mixture was recooled to -78 °C and $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.615 mL, 0.308 mmol) was then added dropwise. Stirring at -78 °C was continued for 10 min and, as before, at 0 °C for 15 min. Finally, the mixture was cooled to -78 °C, and a solution of PhSeCl (62.0 mg, 0.324 mmol) in THF (2 mL) was injected dropwise. After 1 h at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with Et_2O (50 mL), and washed with saturated aqueous NH_4Cl (twice) and brine. The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:5 EtOAc-hexane, gave

10.5 (80 mg, 62%) as a yellow oil, which was used the same day: exact mass (electrospray) *m/z* calcd for $C_{30}H_{31}NNaO_4{}^{80}Se_2$ 652.0476, found 652.0472.

3,7-Dihydro-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (10.6).

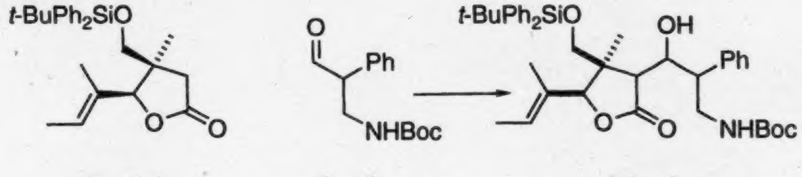


10.5 **10.6**

NaHCO$_3$ (24.0 mg, 0.286 mmol) and NaIO$_4$ (140 mg, 0.655 mmol) were added to a vigorously stirred solution of **10.5** (90.5 mg, 0.144 mmol) in 6:1 MeOH-water (7 mL). After 5.5 h the mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were dried (Na$_2$SO$_4$) and evaporated. Flash chromatography the residue over silica gel (0.7 x 20 cm), using 1:40 MeOH-CH$_2$Cl$_2$, gave **10.6** (12.8 mg, 42%) as a white solid: mp 195-198 °C; FTIR (MeOH-acetone, cast) 2918, 2463, 1646, 1605, 1577, 1550, 1501 cm^{-1}; ^{1}H NMR (CD$_3$OD, 500 MHz) δ 3.19 (t, *J* = 8.7 Hz, 2 H), 4.69 (t, *J* = 8.7 Hz, 2 H), 7.27-7.32 (m, 1 H), 7.34-7.41 (m, 2 H), 7.44-7.48 (m, 2 H), 7.54 (s, 1 H), ^{13}C NMR (CD$_3$OD, 100.6 MHz) (four signals are not observed in this spectrum) δ 26.9 (t), 72.5 (t), 106.3

(s), 128.2 (d), 129.2 (d), 130.4 (d), 136.6 (s); exact mass *m/z* calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0786.

[3-[(4*R,5*S**)-4-[(*tert*-Butyldiphenylsilanyl)oxymethyl]tetrahydro-4-methyl-5-[(1*E*)-1-methyl-1-propenyl]-2-oxofuran-3-yl]-3-hydroxy-2-phenylpropyl]-carbamic Acid *tert*-Butyl Ester (11.1).**

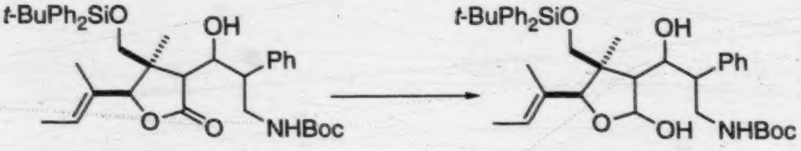


7.14 **9.8** **11.1**

BuLi (2.5 M in hexanes, 1.6 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.55 mL, 3.9 mmol) in THF (16 mL). Stirring at 0 °C was continued for 15 min, and the solution was then cooled to -78 °C. A solution of **7.14** (0.5520 g, 1.306 mmol) in THF (16 mL) was added dropwise to the LDA solution. The mixture was stirred at -78 °C for 30 min, the dry ice-acetone bath was changed to an ice bath, and stirring was continued for 40 min. The mixture was recooled to -78 °C and a solution of **9.8** (0.490 g, 1.97 mmol) and HMPA (0.34 mL, 2.0 mmol) in THF (10 mL) was added dropwise. Stirring at -78 °C was continued for 90 min, and saturated aqueous NH_4Cl (5 mL) was added, followed by Et_2O (100 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl (twice) and brine, dried (Na_2SO_4)

and evaporated. Flash chromatography the residue over silica gel (1.8 x 40 cm), using 1:8 to 1:5 EtOAc-hexane, gave starting lactone **7.14** (0.160 g, 29%) and **11.1** (0627 g, 71%) as a mixture of diastereoisomers: FTIR ($CDCl_3$, cast) 3355, 2965, 2931, 2859, 1763, 1711, 1689, 1589, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82-1.58 (m, 27 H), 2.53 (s, 0.7 H), 2.96-4.30 (m, 3.5 H), 3.09 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 84.4 Hz, 1.4 H), 3.58 (dt, J = 10.7, 3.2 Hz, 0.7 H), 4.16 (d, J = 10.7 Hz, 0.7 H), 4.70-4.83 (m, 1.1 H), 4.91 (s, 0.7 H), 4.98-5.06 (m, 0.2 H), 5.31-5.42 (m, 0.1 H), 5.47 (q, J = 6.7 Hz, 0.7 H), 5.52-5.61 (m, 0.2 H), 7.14-7.65 (m, 16 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, major diastereoisomer only) δ 12.7 (q), 13.7 (q), 16.1 (q), 19.0 (s), 26.7 (q), 28.3 (q), 42.6 (t), 47.0 (s), 48.7 (d), 48.8 (d), 67.9 (t), 67.7 (d), 80.4 (s), 89.7 (d), 122.1 (d), 127.0 (d), 127.5 (d), 127.8 (d), 128.4 (d), 129.0 (d), 129.2 (s), 129.5 (d), 132.8 (s), 133.0 (s), 135.5 (d), 135.6 (d), 140.8 (s), 158.0 (s), 176.4 (s); exact mass (electrospray) *m/z* calcd for $C_{40}H_{53}NNaO_6Si$ 694.3540, found 694.3536.

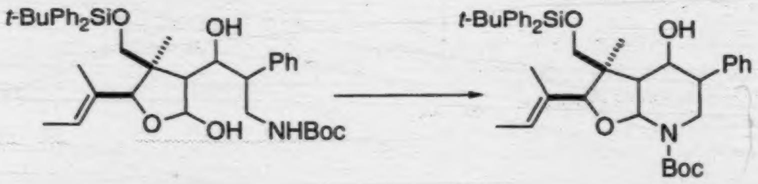
[3-[(4*R,5*S**)-4-[(*tert*-Butyldiphenylsilanyl)oxymethyl]tetrahydro-2-hydroxy-4-methyl-5-[(1*E*)-1-methyl-1-propenyl]furan-3-yl]-3-hydroxy-2-phenylpropyl]-carbamic acid *tert*-Butyl Ester (11.2).**



11.1 **11.2**

DIBAL-H (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **11.1** (284 mg, 0.423 mmol) in CH_2Cl_2 (19 mL). Stirring at -78 °C was continued for 2.5 h, and 3:1 MeOH-water (4 mL) was added dropwise. The cooling bath was removed and stirring was continued for 1 h. The mixture was filtered through a pad of Celite (3 x 3 cm), using EtOAc (80 mL) as a rinse, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for 4 h to afford crude **11.2** (286 mg, 100%), which was a mixture of diastereoisomers and was used without further purification: exact mass (electrospray) *m/z* calcd for $C_{40}H_{55}NNaO_6Si$ 696.3696, found 696.3690.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]hexahydro-4-hydroxy-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (11.3a,b).**



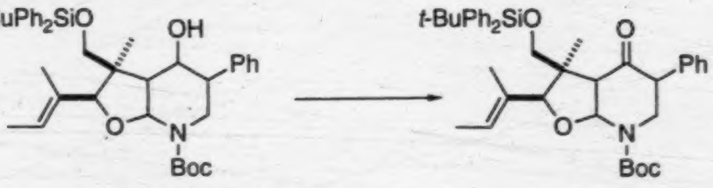
11.2 **11.3a,b**

TsOH.pyridine (148 mg, 0.589 mmol) was added in one portion to a stirred solution of **11.2** (286 mg, 0.423 mmol) in THF (30 mL). The mixture was lowered into an oil bath set at 45 °C and stirring was continued for 15 h. The mixture was cooled to room temperature, diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 40 cm), using 1:6 to 1:4 EtOAc-hexane, gave **11.3** as two fractions: fraction A (**11.3a**, less polar, 150 mg, 54%) and fraction B (**11.3b**, more polar, 76 mg, 27%).

Fraction A (**11.3a**) had: mp 77-80 °C; FTIR (CH_2Cl_2, cast) 3517, 3070, 2962, 2930, 2889, 2858, 1703, 1589 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.10 (s, 9 H), 1.45 (s, 3 H), 1.47 (s, 12 H), 1.50 (d, J = 6.8 Hz, 3 H), 2.26 (d, J = 7.9 Hz, 1 H), 2.34 (s, 1 H), 2.78 (dd, J = 12.2, 3.2 Hz, 1 H), 3.22 [d (formally part of AB q), J = 10.3 Hz, 1 H], 3.42-3.74 (m containing part of AB q, 2 H), 3.84-4.14 (m, 2 H), 4.34 (s, 1 H), 5.49 (q, J = 6.8 Hz, 1 H), 5.61-5.87 (m, 1 H), 7.25-7.50 (m, 11 H), 7.62-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 12.8 (q), 14.3 (q), 18.1 (q), 19.6 (s), 27.2 (q), 28.4 (q), 37.7 (t), 45.9 (d), 47.0 (d), 49.7 (s), 68.0 (t), 69.3 (d), 80.7 (s), 82.5 (d), 88.2 (d), 119.8 (d), 127.3 (d), 128.08 (d), 128.12 (d), 128.4 (d), 128.9 (d), 130.1 (d), 130.2 (d), 133.4 (s), 133.9 (s), 134.0 (s), 135.98 (d), 136.02 (d), 141.4 (s), 155.4 (s); exact mass (electrospray) *m/z* calcd for $C_{40}H_{53}NNaO_5Si$ 678.3591, found 678.3590.

Fraction B (**11.3b**) had: mp 54-56 °C; FTIR (CH_2Cl_2, cast) 3465, 3070, 2963, 2930, 2858, 1703, 1602, 1589 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.01 (s, 9 H), 1.29 (s, 3 H), 1.39 (s, 9 H), 1.46 (s, 3 H), 1.54 (d, J = 6.8 Hz, 3 H), 2.48-2.58 (m, 1 H), 3.22 (d, J = 4.8 Hz, 1 H), 3.39 (dd, J = 13.2, 4.0 Hz, 1 H), 3.42 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 156.3 Hz, 2 H), 4.02-4.16 (m, 2 H), 4.25 (s, 1 H), 5.49 (q, J = 6.8 Hz, 1 H), 6.03 (br s, 1 H), 7.24-7.49 (m, 12 H), 7.57-7.65 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.1 (q), 14.0 (q), 19.1 (q), 19.6 (s), 27.1 (q), 28.3 (q), 42.6 (t), 45.1 (d), 46.7 (d), 51.1 (s), 67.6 (t), 68.5 (d), 80.5 (s), 83.5 (d), 88.1 (d), 121.5 (d), 127.5 (d), 128.0 (d), 128.1 (d), 128.9 (d), 129.9 (d), 130.0 (d), 130.2 (d), 132.5 (s), 133.8 (s), 134.0 (s), 136.0 (d), 139.5 (s), 155.3 (s); exact mass (electrospray) m/z calcd for $C_{40}H_{53}NNaO_5Si$ 678.3591, found 678.3589.

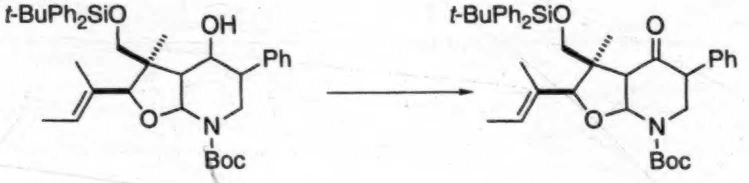
(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (11.4a).**



11.3a **11.4a**

Dess-Martin reagent (128 mg, 0.302 mmol) was added in one portion to a stirred solution of **11.3a** (less polar diastereoisomer) (132 mg, 0.201 mmol) in CH_2Cl_2 (18 mL). After 30 min, another portion of Dess-Martin reagent (128 mg, 0.302 mmol) was added. Stirring was continued for 2 h, and the mixture was diluted with Et_2O (100 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 40 cm), using 1:9 EtOAc-hexane, gave **11.4a** (126 mg, 96%) as a solid: mp 57-59 °C; FTIR (CH_2Cl_2, cast) 3070, 2964, 2931, 2858, 1704, 1589 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.39 (s, 9 H), 1.41 (s, 3 H), 1.79 (s, 12 H), 1.84 (d, J = 6.8 Hz, 3 H), 3.66 (d, J = 7.3 Hz, 1 H), 3.71 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 120.6 Hz, 2 H), 3.81-4.09 (m, 2 H), 4.63 (s, 1 H), 4.60-4.77 (m, 1 H), 5.84 (q, J = 6.8 Hz, 1 H), 6.60 (br s, 1 H), 7.44-7.52 (m, 2 H), 7.56-7.78 (m, 9 H), 7.91-7.98 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.2 (q), 14.0 (q), 19.7 (s), 20.0 (q), 27.2 (q), 28.5 (q), 43.2 (t), 53.9 (s), 54.8 (d), 56.1 (d), 68.3 (t), 81.3 (s), 84.4 (d), 91.5 (d), 122.8 (d), 127.8 (d), 128.10 (d), 128.13 (d), 129.0 (d), 129.2 (d), 130.2 (d), 131.6 (s), 133.8 (s), 133.9 (s), 136.08 (d), 136.10 (d), 136.8 (s), 154.4 (s), 207.7 (s); exact mass (electrospray) m/z calcd for $C_{40}H_{51}NNaO_5Si$ 676.3434, found 676.3439.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (11.4b).**

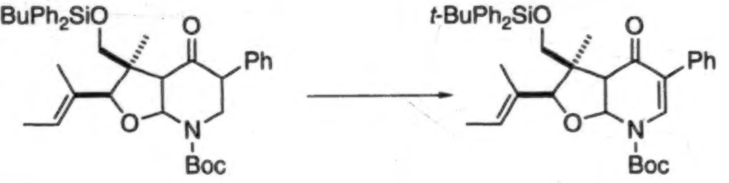


11.3b **11.4b**

Dess-Martin reagent (146 mg, 0.344 mmol) was added in one portion to a stirred solution of **11.3b** (more polar diastereoisomer) (105 mg, 0.160 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 3 h, and the mixture was diluted with Et_2O (40 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:9 EtOAc-hexane, gave **11.4b** (89 mg, 85%) as an oil: FTIR (CH_2Cl_2, cast) 3361, 2974, 2931, 2859, 1746, 1708, 1589 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.08 (s, 3 H), 1.09 (s, 9 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.55 (d, J = 6.8 Hz, 3 H), 3.33 (d, J = 6.4 Hz, 1 H), 3.39 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 152.1 Hz, 2 H), 3.92-4.02 (m, 2 H), 4.07 (dd, J = 9.0, 7.0 Hz, 1 H), 4.44 (s, 1 H), 5.57 (q, J = 6.8 Hz, 1 H), 6.23 (d, J = 5.1 Hz, 1 H), 7.16-7.22 (m, 2 H), 7.29-7.49 (m, 9 H), 7.61-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.1 (q), 14.1 (q), 19.6 (s), 20.0 (q), 27.1 (q), 28.3 (q), 47.7 (t), 52.8 (s), 53.9 (d), 56.6 (d), 66.7 (t), 81.1 (s), 85.5 (d), 89.8 (d), 122.2 (d), 127.8 (d), 128.07 (d), 128.13 (d), 128.8 (d), 129.3 (d), 130.1 (d), 130.2 (d), 131.6 (s), 133.6 (s), 133.7 (s), 136.0 (d), 136.1 (d), 137.1 (s), 154.8 (s), 207.3 (s); exact mass (electrospray) m/z calcd for $C_{40}H_{51}NNaO_5Si$

676.3434, found 676.3437.

(2R*,3S*)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-2,3,3a,7a-tetrahydro-3-methyl-2-[(1E)-1-methyl-1-propenyl]-4-oxo-5-phenyl-4H-furo[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (11.5).



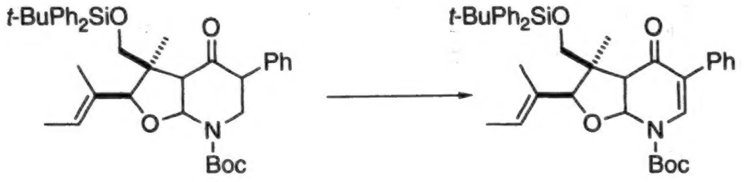
11.4a **11.5**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.30 mL, 0.15 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketone **11.4a** (less polar diastereoisomer) (87.0 mg, 0.133 mmol) in THF (4 mL). Stirring at -78 °C was continued for 15 min, and then at 0 °C (mixture transferred to an ice bath) for 15 min. The mixture was recooled to -78 °C, and a solution of PhSeCl (30.0 mg, 0.157 mmol) in THF (2 mL) was added dropwise. After 30 min at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with Et_2O (40 mL), and washed with saturated aqueous NH_4Cl and brine. The organic phase was dried (Na_2SO_4) and evaporated to give the crude selenide (117 mg), which was used directly for the next step.

Pyridine (0.080 mL, 0.99 mmol) and H_2O_2 (30%, 0.13 mL, 1.1 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (117 mg) in CH_2Cl_2 (15 mL).

The cooling bath was removed and stirring was continued for 40 min. The mixture was diluted with Et_2O (100 mL), and washed successively with water, saturated aqueous $CuSO_4$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:12 EtOAc-hexane, gave **11.5** (64 mg, 74%) as a white solid: mp 60-63 °C; FTIR (CD_2Cl_2, cast) 3070, 2960, 2931, 2857, 1729, 1662, 1619 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.10 (s, 9 H), 1.12 (s, 3 H), 1.50 (s, 3 H), 1.53 (s, 9 H), 1.55 (d, J = 6.8 Hz, 3 H), 3.46 (d, J = 7.7 Hz, 1 H), 3.47 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 93.2 Hz, 2 H), 4.19 (s, 1 H), 5.50 (q, J = 6.8 Hz, 1 H), 6.06 (d, J = 7.7 Hz, 1 H), 7.26-7.48 (m, 11 H), 7.63-7.73 (m, 4 H), 7.92 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 13.2 (q), 13.9 (q), 19.2 (q), 19.6 (s), 27.2 (q), 28.2 (q), 54.4 (s), 54.6 (d), 68.2 (t), 84.0 (s), 84.7 (d), 90.2 (d), 119.7 (s), 122.8 (d), 127.5 (d), 128.05 (d), 128.08 (d), 128.5 (d), 128.8 (d), 130.11 (d), 130.15 (d), 131.3 (s), 133.78 (s), 133.81 (s), 134.9 (s), 136.1 (d), 141.4 (d), 152.0 (s), 192.1 (s); exact mass (electrospray) *m/z* calcd for $C_{40}H_{49}NNaO_5Si$ 674.3278, found 674.3279.

(2*R**,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-2,3,3a,7a-tetrahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenyl-4*H*-furo[2,3-*b*]-pyridine-7-carboxylic Acid *tert*-Butyl Ester (11.5).

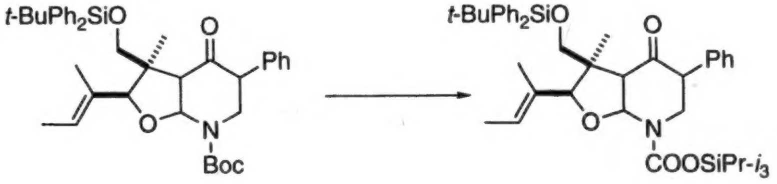


11.4b **11.5**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.25 mL, 0.125 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketone **11.4b** (72.0 mg, 0.110 mmol) in THF (3.6 mL). Stirring at -78 °C was continued for 15 min, and then at 0 °C (mixture transferred to an ice bath) for 15 min. The mixture was recooled to -78 °C, and a solution of PhSeCl (25.0 mg, 0.131 mmol) in THF (1.6 mL) was added dropwise. After 30 min at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with Et_2O (40 mL), and washed with saturated aqueous NH_4Cl and brine. The organic phase was dried (Na_2SO_4) and evaporated to give the crude selenide (89 mg), which was used directly for the next step.

Pyridine (0.060 mL, 0.74 mmol) and H_2O_2 (30%, 0.10 mL, 0.88 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (89 mg) in CH_2Cl_2 (12 mL). The cooling bath was removed and stirring was continued for 40 min. The mixture was diluted with Et_2O (100 mL), and washed successively with water, saturated aqueous $CuSO_4$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:15 EtOAc-hexane, gave **11.5** (17 mg, 24%), which was identical to material obtained in the less polar series.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid Tri-isopropylsilyl Ester (12.1a).**



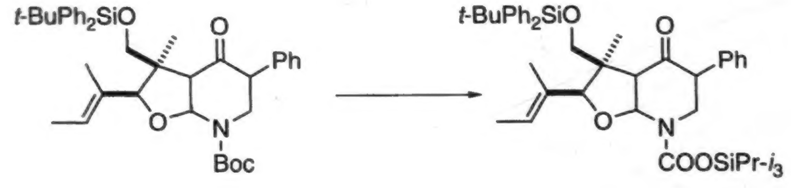
11.4a **12.1a**

2,6-Lutidine (0.34 mL, 2.9 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.63 mL, 2.3 mmol) were added successively to a stirred solution of **11.4a** (less polar diastereoisomer) (189 mg, 0.289 mmol) in CH_2Cl_2 (25 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 45 °C, and stirring was continued for 60 h. The mixture was cooled, diluted with Et_2O (100 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 35 cm), using 1:25 EtOAc-hexane, gave **12.1a** (218 mg, 100%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3070, 2944, 2866, 1692, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99-1.12 (m, 30 H), 1.32 (septet, J = 7.5 Hz, 3 H), 1.43 (s, 3 H), 1.50 (d, J = 6.4 Hz, 3 H), 3.31-3.92 (m, 3 H), 3.35 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 161.8 Hz, 2 H), 4.20-4.60 (m, 2 H), 5.40-5.60 (m, 1 H), 6.20-6.50 (m, 1 H), 7.10-7.44 (m, 11 H), 7.56-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, major rotamer only) δ 12.1 (d), 12.3 (q), 12.9 (q), 17.8 (q), 19.4 (s), 19.6 (q), 27.0 (q), 43.2 (s), 53.5 (t), 54.2 (d), 55.6 (d), 67.7 (t), 84.9 (d), 90.7 (d), 122.2 (d), 127.6 (d), 127.7 (d), 128.6 (d), 129.7 (d), 129.8 (d), 131.0 (s), 133.3 (s), 133.4 (s), 135.6 (d), 135.7 (d), 153.8 (s), 207.2 (s); exact mass (electrospray) m/z calcd for $C_{45}H_{63}NNaO_5Si_2$ 776.4137, found 776.4133.

When the ^{1}H NMR spectrum was run at 45 °C many signals coalesced: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99-1.12 (m, 30 H), 1.30 (septet, J = 7.5 Hz, 3 H), 1.41 (s, 3 H), 1.48 (d, J = 6.6 Hz, 3 H), 3.34 (d, J = 7.0 Hz, 1 H), 3.35 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 130.1 Hz, 2 H), 3.54 (br s, 1 H), 3.71 (br s, 1 H), 4.26 (s, 1 H), 4.42 (br s, 1 H), 5.39-5.53 (m, 1 H), 6.31 (br s, 1 H), 7.11 (d, J = 7.3 Hz, 2 H), 7.21-7.41 (m, 9 H), 7.57 (d, J = 7.0 Hz, 4 H). At -60 °C (and at -20 °C) well separated sets of signals appeared (values for -60 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89-1.12 (m, 30 H), 1.24 (septet, J = 7.3 Hz, 3 H), 1.35 (s, 1.5 H), 1.36 (s, 1.5 H), 1.45 (d, J = 6.7 Hz, 3 H), 3.02-3.13 (m, 1 H), 3.30-3.82 (m, 4 H), 4.22-4.34 (m, 1.5 H), 4.40-4.50 (m, 0.5 H), 5.43 (q, J = 6.7 Hz, 0.5 H), 5.53 (q, J = 6.7 Hz, 0.5 H), 6.26 (d, J = 7.0 Hz, 0.5 H), 6.40 (d, J = 7.7 Hz, 0.5 H), 7.02-7.09 (m, 2 H), 7.20-7.42 (m, 9 H), 7.48-7.55 (m, 4 H).

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-**

propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid Triisopropylsilyl Ester (12.1b).



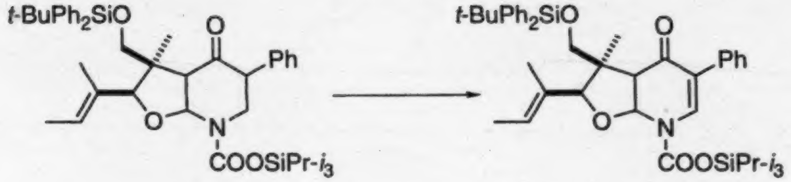
11.4b **12.1b**

2,6-Lutidine (0.045 mL, 0.39 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.075 mL, 0.28 mmol) were added successively to a stirred solution of **11.4b** (28.0 mg, 0.0428 mmol) in CH_2Cl_2 (3 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 45 °C, and stirring was continued for 2 days. The mixture was cooled, diluted with Et_2O (20 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc-hexane, gave **12.1b** (32.3 mg, 100%) as a colorless oil: FTIR ($CDCl_3$, cast) 3070, 2944, 2892, 2866, 1723, 1692, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98-1.13 (m, 30 H), 1.29 (septet, J = 7.4 Hz, 3 H), 1.44 (s, 3 H), 1.50 (d, J = 6.7 Hz, 3 H), 3.18 [d (formally part of AB q), J = 10.2 Hz, 1 H], 3.37 (d, J = 4.9 Hz, 1 H), 3.51 [d (broad signal, formally part of AB q), J = 8.4 Hz, 1 H], 3.99-4.16 (m, 3 H), 4.42 (s, 1 H), 5.56 (br s, 1 H), 6.14-6.45 (m, 1 H), 7.11-7.44 (m, 11 H), 7.55-7.61 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) (major rotamer only) δ 12.0 (d), 12.3 (q), 12.9 (q), 17.8 (q), 19.4 (s), 19.8 (q), 26.9 (q), 47.5 (t), 52.4

(s), 53.5 (d), 67.0 (t), 86.0 (d), 121.9 (d), 127.7 (d), 128.7 (d), 129.8 (d), 131.0 (s), 133.2 (s), 135.6 (d), 135.7 (d), 154.1 (s), 206.7 (s); exact mass (electrospray) *m/z* calcd for $C_{45}H_{63}NNaO_5Si_2$ 776.4143, found 776.4147.

When the ^1H NMR spectrum was run at 45 °C many signals coalesced: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.14 (m, 30 H), 1.30 (septet *J* = 7.4 Hz, 3 H), 1.44 (s, 3 H), 1.51 (d, *J* = 6.6 Hz, 3 H), 3.36 (AB q, *J* = 10.3 Hz, $\Delta\nu_{AB}$ = 130.3 Hz, 2 H), 3.37 (d, *J* = 6.1 Hz, 1 H), 3.99-4.15 (m, 3 H), 4.41 (s, 1 H), 5.50-5.62 (m, 1 H), 6.29 (br s, 1 H), 7.17 (d, *J* = 7.1 Hz, 2 H), 7.23-7.44 (m, 9 H), 7.55-7.62 (m, 4 H). At -60 °C (and at -20 °C) well separated sets of signals appeared (values for -60 °C): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84-1.04 (m, 30 H), 1.21 (septet, *J* = 7.5 Hz, 3 H), 1.34 (s, 3 H), 1.41-1.48 (m, 3 H), 3.02-3.11 (m, 1 H), 3.28-3.44 (m, 2 H), 3.77-3.92 (m, 1 H), 3.95-4.06 (m, 1 H), 4.12-4.23 (m, 1 H), 4.36 (s, 0.5 H), 4.38 (s, 0.5 H), 5.49 (q, *J* = 7.0 Hz, 0.5 H), 5.61 (q, *J* = 7.0 Hz, 0.5 H), 6.17 (d, *J* = 5.7 Hz, 0.5 H), 6.30 (d, *J* = 6.0 Hz, 0.5 H), 7.08-7.14 (m, 2 H), 7.23-7.43 (m, 9 H), 7.47-7.55 (m, 4 H).

(2*R**,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-2,3,3a,7a-tetrahydro-3-methyl-2-(1-methyl-1-propenyl)-4-oxo-5-phenyl-4*H*-furo[2,3-*b*]pyridine-7-carboxylic Acid Triisopropylsilyl Ester (12.2).

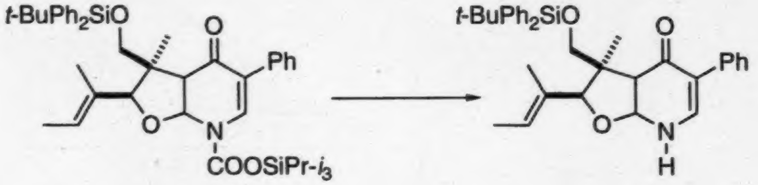


12.1a **12.2**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.60 mL, 0.30 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketone **12.1a** (208 mg, 0.275 mmol) in THF (10 mL), and stirring at -78 °C was continued for 90 min. A solution of PhSeCl (58.5 mg, 0.305 mmol) in THF (5 mL) was added dropwise. After 45 min at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with Et_2O (100 mL), and washed with saturated aqueous NH_4Cl and brine. The organic phase was dried (Na_2SO_4) and evaporated to give the crude selenide (266 mg), which was used directly for the next step.

Pyridine (0.15 mL, 1.9 mmol) and H_2O_2 (30%, 0.24 mL, 2.1 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (266 mg, ca 0.175 mmol) in CH_2Cl_2 (30 mL). The cooling bath was removed and stirring was continued for 35 min. The mixture was diluted with EtOAc (80 mL) and washed successively with water, saturated aqueous $CuSO_4$, water and brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for 30 min to afford the crude **12.2** (200 mg), which was used directly for next step without purification.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,3a,7,7a-tetrahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridine-4-one (12.3).**

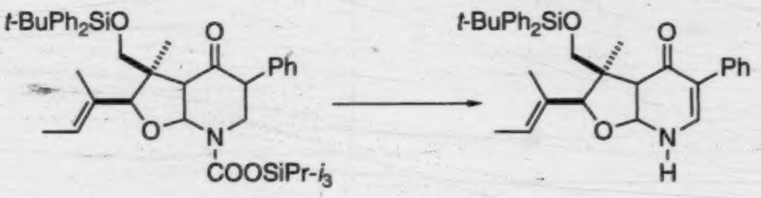


12.2 **12.3**

Bu_4NF (1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred and cooled (0 °C) solution of crude **12.2** (200 mg) in THF (20 mL). After 5 min, the mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with EtOAc (60 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:3 EtOAc-hexane, gave **12.3** (79.8 mg, 53% from **12.1a**) as a colorless oil: FTIR (CH_2Cl_2 cast) 3247, 3049, 2960, 2930, 2858, 1826, 1602, 1584 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.08 (s, 9 H), 1.17 (s, 3 H), 1.62 (d, J = 6.7 Hz, 3 H), 1.66 (s, 3 H), 2.99 (d, J = 7.9 Hz, 1 H), 3.55 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 18.1 Hz, 2 H), 4.36 (s, 1 H), 5.42 (d, J = 6.3 Hz, 1 H), 5.60 (q, J = 6.7 Hz, 1 H), 5.66 (d, J = 7.9 Hz, 1 H), 7.16-7.48 (m, 12 H), 7.61-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 13.3 (q), 14.5 (q), 19.6 (s), 19.7 (q), 27.2 (q), 52.4 (s), 55.2 (d), 68.4 (t), 86.6 (d), 90.9 (d), 111.4 (s), 122.4 (d), 126.2

(d), 127.96 (d), 127.97 (d), 128.3 (d), 128.4 (d), 129.9 (d), 130.0 (d), 132.6 (s), 133.89 (s), 133.94 (s), 136.2 (d), 136.4 (s), 148.4 (d), 189.7 (s); exact mass (electrospray) *m/z* calcd for $C_{35}H_{41}NNaO_3Si$ 574.2753, found 574.2754.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,3a,7,7a-tetrahydro-3-methyl-2-(1-methyl-1-propenyl)-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (12.3).**



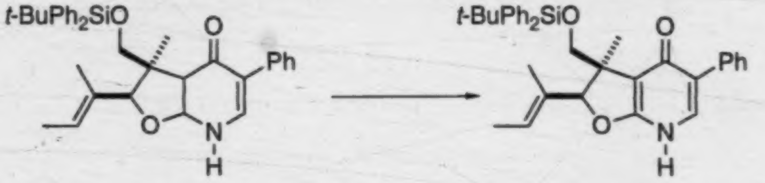
12.1b **12.3**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.10 mL, 0.050 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **12.1b** (32.0 mg, 0.0428 mmol) in THF (2 mL), and stirring at -78 °C was continued for 90 min. A solution of PhSeCl (10 mg, 0.052 mmol) in THF (1 mL) was added dropwise. After 45 min at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with Et_2O (20 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated, to give the crude selenide (44.4 mg), which was used directly for the next step.

Pyridine (0.030 mL, 0.37 mmol) and H_2O_2 (30%, 0.050 mL, 0.44 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (44.4 mg) in CH_2Cl_2 (6 mL).

The cooling bath was removed and stirring was continued for 45 min. The mixture was diluted with EtOAc (20 mL), and washed successively with water, saturated aqueous $CuSO_4$, water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over Al_2O_3 (Grade III), using 1:20 to 1:5 EtOAc-hexane, gave **12.3** (11.5 mg, 49% from **12.1b**), which had the same spectroscopic characteristics as material from the less polar series.

(2*R**,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,7-dihydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (12.4).



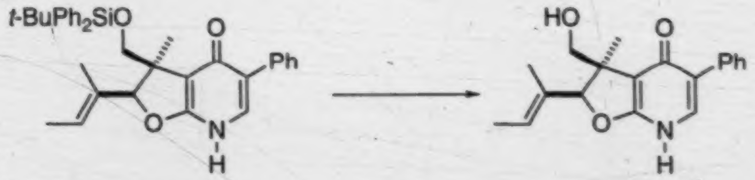
12.3 **12.4**

All steps in this experiment were done with protection from light.

Freshly prepared *t*-BuOCl[41] (0.1 M in CH_2Cl_2, 1.4 mL, 0.14 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **12.3** (31.0 mg, 0.0562 mmol) in CH_2Cl_2, the mixture being protected from light by alumina foil. After 15 min at -78 °C, the solvent was evaporated and the residue was kept under oil pump vacuum for 15 min.

PhMe (5 mL) was injected into the reaction flask (protection from light), followed by DBU (0.080 mL, 0.53 mmol). Stirring was continued for 1 h at room temperature, and the solvent was evaporated. Flash chromatography of the residue over silica gel (0.7 x 20 cm), using 1:3 EtOAc-hexane, gave **12.4** (22 mg, 71%) as a white solid: mp 99-101 °C; FTIR (CH_2Cl_2, cast) 3050, 2960, 2930, 2858, 1827, 1647, 1595, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9 H), 1.35 (s, 3 H), 1.41 (d, J = 6.7 Hz, 3 H), 1.48 (s, 3 H), 3.57 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 144.3 Hz, 2 H), 4.64 (s, 1 H), 5.34 (q, J = 6.7 Hz, 1 H), 7.28-7.67 (m, 15 H), 7.95 (s, 1 H), 9.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.8 (q), 12.9 (q), 19.2 (s), 24.7 (q), 26.9 (q), 49.0 (s), 69.4 (t), 94.1 (d), 110.0 (s), 120.9 (s), 124.2 (d), 126.9 (d), 127.98 (d), 128.01 (d), 128.2 (d), 129.3 (d), 130.3 (d), 130.5 (d), 131.2 (s), 131.3 (s), 131.5 (s), 135.3 (s), 135.5 (d), 135.9 (d), 149.1 (d), 158.5 (s), 167.9 (s); exact mass (electrospray) *m/z* calcd for $C_{35}H_{40}NO_3Si$ 550.2772, found 550.2777.

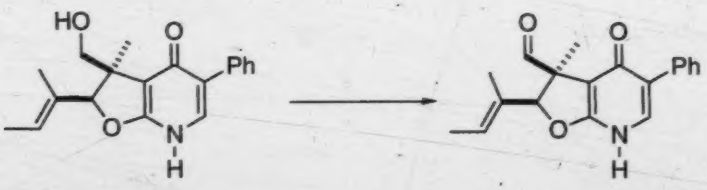
(2*R,3*S**)-3,7-Dihydro-3-hydroxymethyl-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (2).**



12.4 **2**

Bu_4NF (1.0 M in THF, 0.12 mL, 0.12 mmol) was added dropwise to a stirred solution of **12.4** (21.5 mg, 0.0391 mmol) in THF (7 mL). Stirring was continued for 15 min, and then saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (0.9 x 20 cm), using 1:1 EtOAc-hexane, gave **2** (11.8 mg, 97%) as a colorless solid: mp 213-214 °C; FTIR (CH_2Cl_2, cast) 3057, 2926, 2860, 2742, 1695, 1598, 1502 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.51 (s, 3 H), 1.54 (s, 3 H), 1.63 (d, J = 6.8 Hz, 3 H), 3.76 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 13.6 Hz, 2 H), 4.84 (s, 1 H), 5.63 (q, J = 6.8 Hz, 1 H), 7.25-7.31 (m, 1 H), 7.34-7.41 (m, 2 H), 7.50-7.56 (m, 2 H), 7.82 (s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.4 (q), 13.5 (q), 25.7 (q), 50.5 (s), 67.3 (t), 95.3 (d), 111.8 (s), 125.3 (d), 128.0 (d), 129.3 (d), 130.6 (d), 133.7 (s), 137.3 (s); exact mass m/z calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1517.

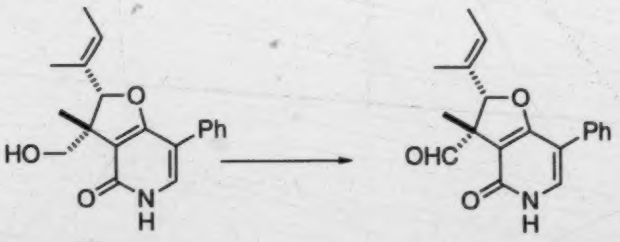
(2*R**,3*R**)-2,3,4,7-Tetrahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-3-carbaldehyde (cladobotryal) (1).



2 **1**

Dess-Martin reagent (30.0 mg, 0.0708 mmol) was added in one portion to a stirred solution of **2** (11.0 mg, 0.0353 mmol) in CH_2Cl_2 (6 mL). After 15 min, saturated aqueous $NaHCO_3$ (10 mL) and 10% aqueous $Na_2S_2O_3$ (5 mL) were added. The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.9 x 25 cm), using 2:3 EtOAc-hexane, gave aldehyde **1** (10.6 mg, 97%) as a solid: mp 95-97 °C; FTIR ($CDCl_3$, cast) 2923, 2859, 2721, 1727, 1648, 1595, 1555, 1501 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.57 (s, 3 H), 1.63 (s, 3 H), 1.65 (d, J = 6.8 Hz, 3 H), 5.01 (s, 1 H), 5.82 (q, J = 6.8 Hz, 1 H), 5.30-5.49 (m, 5 H), 7.78 (s, 1 H), 9.61 (s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.5 (q), 20.7 (q), 59.2 (s), 107.8 (s), 125.5 (d), 128.8 (d), 129.9 (d), 130.8 (d), 131.8 (s), 136.1 (s), 201.2 (d); exact mass m/z calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1363.

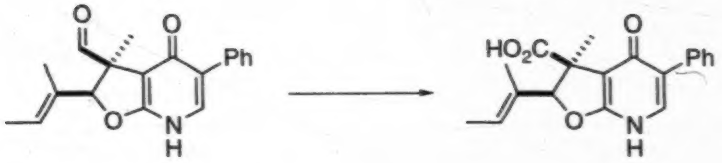
(2*R**,3*R**)-3-Methyl-2-[(*E*)-(1-methylpropenyl)]-4-oxo-7-phenyl-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-3-carboxaldehyde (13.1).



8.6 **13.1**

Dess-Martin reagent (49.0 mg, 0.116 mmol) was added in one portion to a stirred solution of **8.6** (18.0 mg, 0.0578 mmol) in CH_2Cl_2 (4 mL). After 10 min, EtOAc (10 mL) was added followed by saturated aqueous $NaHCO_3$ (with 10% $Na_2S_2O_3$) (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and all the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 25 cm), using 1:50 MeOH-CH_2Cl_2, gave the aldehyde **13.1** (17.5 mg, 98%) as a pale yellow solid: mp 221-222 °C; FTIR (CH_2Cl_2, cast) 2928, 1729, 1652, 1617, 1599, 1578, 1560, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (t, *J* = 1.1 Hz, 3 H), 1.62 (dt, *J* = 6.8, 0.8 Hz, 3 H), 1.64 (s, 3 H), 4.96 (s, 1 H), 5.69 (q of multiplets, *J* = 6.8 Hz, 1 H), 7.27-7.43 (m, 3 H), 7.49-7.55 (m, 2 H), 7.57 (s, 1 H), 9.59 (s, 1 H); the NH signal was not observed within the region examined (δ 0-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.1 (q), 13.3 (q), 19.5 (q), 57.7 (s), 98.3 (d), 110.7 (s), 110.8 (s), 124.5 (d), 127.5 (d), 127.6 (d), 128.8 (d), 129.5 (s), 132.6 (s), 136.2 (d), 162.3 (s), 167.9 (s), 199.2 (d); exact mass *m/z* calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1358.

(2*R,3*R**)-2,3,4,7-Tetrahydro-3-methyl-2-[(*E*)-1-methylpropenyl]-4-oxo-5-phenyl-furo[2,3-*b*]pyridine-3-carboxylic Acid (13.2).**



1 **13.2**

A solution of $NaClO_2$ (13.2 mg, 0.117 mmol) and $NaH_2PO_4.H_2O$ (17.1 mg, 0.124 mmol) in water (0.25 mL) was added over 1 min to a stirred and cooled (0 °C) solution of cladobotryal **1** (4.5 mg, 0.0145 mmol) in 4:4:1 MeCN-*t*-BuOH-2-methyl-2-butene (1 mL). The mixture was stirred for an additional 15 min at 0 °C, and then extracted with EtOAc (10 mL). The extract was washed with brine (2 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 20 cm), using 1:5 MeOH-CH_2Cl_2, gave **13.2** (3.6 mg, 76%) as a white solid: mp 190-192 °C; FTIR (acetone, cast) 3091, 2925, 2854, 2659, 1703, 1651, 1615, 1502 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.50 (s, 3 H), 1.60 (d, J = 6.7 Hz, 3 H), 1.70 (s, 3 H), 5.02 (s, 1 H), 5.70 (q, J = 6.7 Hz, 1 H), 7.26-7.42 (m, 3 H), 7.55-7.62 (m, 2 H), 7.78 (s, 1 H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 11.7 (q), 13.2 (q), 27.2 (q), 56.0 (s), 109.6 (s), 126.7 (d), 127.9 (d), 128.8 (d), 129.9 (d), 133.2 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{20}NO_4$ 326.1387, found 326.1389.

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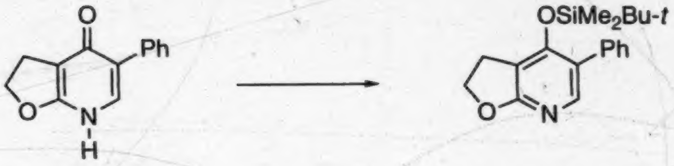
33 Since some of the expected ^{13}C NMR signals of **10.6** could not be detected, we prepared the corresponding *O*-(*tert*-butyldimethylsilyl) derivative, for which all the expected ^{13}C NMR signals could be seen:

4-[(*tert*-Butyldimethylsilanyl)oxy]-2,3-dihydro-5-phenylfuro-[2,3-*b*]pyridine. (Derivative of 10.6)



10.6 --

t-BuMe$_2$SiCl (78.5 mg, 0.521 mmol) and Et$_3$N (0.10 mL, 0.71 mmol) were added successively to a stirred solution of **10.6** (18.5 mg, 0.0868 mmol) in PhMe (8 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 115 °C, and stirring was continued for 2 h. The mixture was cooled and evaporated. Flash chromatography the residue over silica gel (0.7 x 15 cm), using 1:3 EtOAc-hexane, gave the *O*-silylated (reference 34) derivative (19 mg, 67%) as a colorless oil: FTIR (CD$_3$OD, cast) 2953, 2929, 2885, 2859, 2025, 1603, 1501 cm^{-1}; ^{1}H NMR (CD$_2$Cl$_2$, 500 MHz) δ -0.21 (s, 6 H), 0.84 (s, 9 H), 3.23 (t, J = 8.7 Hz, 2 H), 4.60 (t, J = 8.7 Hz, 2 H), 7.28-7.45 (m, 5 H), 7.83 (s, 1 H); ^{13}C NMR (CD$_2$Cl$_2$, 125.7 MHz) δ -4.2 (q), 18.5 (s), 25.6 (q), 27.6 (t), 69.7 (t), 109.6 (s), 125.6 (s), 127.4 (d), 128.6 (d), 130.3 (d), 136.6 (s), 148.8 (d), 157.9 (s), 170.5 (s); exact mass m/z calcd for C$_{19}$H$_{25}$NO$_2$Si 327.1655, found 327.1651.

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6 NMR SPECTRA

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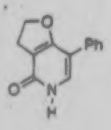

5.6